DEVELOPMENT OF NOVEL METHODOLOGIES FOR THE CONSTRUCTION OF C-HETERO BOND

A Thesis submitted to the University of North Bengal

For the Award of

Doctor of Philosophy

in

Chemistry

By

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Guide

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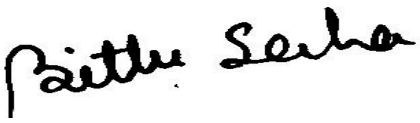
Dedicated to my beloved parents…

DECLARATION

I declare that the thesis entitled "**DEVELOPMENT OF NOVEL METHODOLOGIES FOR THE CONSTRUCTION OF C-HETERO BOND"** has been prepared by me under the guidance of Prof. Pranab Ghosh, Department of Chemistry, University of North Bengal. No part of this thesis has formed the basis for the award of any degree or fellowship previously.



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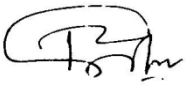
CERTIFICATE

I certify that **Mr. BITTU SAHA** has prepared the thesis entitled "**DEVELOPMENT OF NOVEL METHODOLOGIES FOR THE CONSTRUCTION OF C-HETERO BOND**", for the award of Ph.D. Degree of the University of North Bengal, under my guidance. He has carried out the research work at the Department of Chemistry, University of North Bengal. No part of this thesis has formed the basis for the award of any degree or fellowship previously.



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Acknowledgement

This thesis is a compilation of my research work carried out under the supervision of Prof.Pranab Ghosh, Professor, Department of Chemistry, University of North Bengal during the period of 2013 to 2018. It comprises with the studies of C-hetero bond forming reaction.

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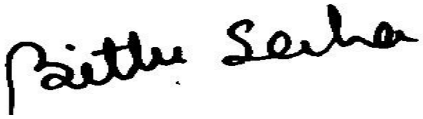

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Abstract

Chapter I: A general introduction of C-hetero bonds:

Though, for most of organic compounds C-C bond is the backbone, but their functions are derived by the presence of hetero atoms such as oxygen, nitrogen and sulphur etc. in the moiety. These molecules act as most imperious subtype of organic molecules in the dominion of biomedical science, pharmaceutical and also in material sciences. For example, suitable derivatives of C-hetero molecules basically C-N heteroatom bonds act as important fragments for many naturally occurring and also in synthetic drugs to heal diseases, non-classical isosteres for the carboxylic acid moiety of biologically active molecules and are also useful to ligand modeling for transition metal complexes in both biological and non-biological system etc. The vast importance and wide scope of carbon-hetero bond make the author to carry out the methodological work on C-hetero bond formation reactions.

Chapter II: Fe_3O_4-CTAB nanoparticles catalyzed an efficient synthesis of nitriles from aldehydes:

Section A: Chapter II (section A) is comprised with the basic information of nitriles and also a methodological literature review for their synthesis. Nitriles are useful intermediate for many organic transformation and heterocyclic moiety formations. For this a number of methodologies using different catalysts or precursors are available. But drawbacks associating with those existing methodologies make a scope to develop a new protocol for their synthesis.

Section B: ChapterII (section B) contains Fe_3O_4-CTAB nanoparticles catalysed synthesis of nitriles from aromatic, aliphatic and hetero aromatic aldehydes under mild reaction condition. Here, a reaction between an aldehyde (0.5 mmol), hydroxylamine hydrochloride (0.75mmol) Fe_3O_4 -CTAB nanoparticles (5.7 mg) is carried out in dry DMF (5 ml) under reflux condition. This reaction protocol gives excellent yield of nitriles for both aromatic and heteroaromatic aldehydes except for the aliphatic aldehyde which give relatively lower yield.

Chapter III: Reactions catalysed by 3, 5 Di-nitrobenzoic Acid Derived Copper (II) Complex:

Section A: Chapter III (section A) contains general information of imidazole and the synthetic literature survey for the preparation of 2, 4, 5-trisubstituted imidazole. Imidazoles has N-

containing heteroaromatic moiety. They serve as a major building block of many biological active compounds, amphiphilic molecule for drug delivery and also for treatment of many parasitic decreases. Their importance attracts researcher to find a suitable and most efficient protocol for the preparation of imidazole. Several reaction methodologies are available for the preparation but most of them are associated with drawbacks. So, there is always a scope to find a new protocol for the preparation.

Section B: Chapter III (section B) deals with the preparation of 2, 4, 5-trisubstituted imidazole using 3, 5 Di-nitrobenzoic acid derived Copper (II) Complex as a catalyst under mild and solvent free reaction condition. We used reaction of benzil/benzoin (0.5 mmol), aldehydes (0.5mmol), NH_4OAc (1mmol), catalyst (2.5 mol %) and silica-gel (750 mg) at 70^0C for our reaction protocol. This protocol stands well for aromatic, aliphatic and heteroaromatic aldehydes. It gives excellent to good yield of desired product. This protocol can easily omits certain drawbacks such as tedious work-up process, usage of hazardous catalyst and also the formation of other unwanted side products etc.

Chapter IV: Highly efficient polymeric-Cu (II) catalysed one pot multi-component synthesis of substituted N-heterocycles *via* double condensation/ tandem oxidation-cyclisation/elimination-cyclisation reactions from diverse starting precursors under milder reaction conditions.

Section A: ChapterIV (section A) compares with the general introduction and methodological literature survey about the synthesis of pyrazine and quinoxaline. Pyrazine is an aromatic heterocyclic moiety contains nitrogen at 1 and 4 position of the heterocyclic ring. It is an important component of aromas in vegetables, fruits and wines. It also serves important building block for biological potent molecules. Whereas quinoxaline has a fused heteroaromatic structure in which nitrogen atoms are present at 1 and 4 position of one of the two fused ring. They show an inhabiting effect against of transplantable tumors and also for Gram-positive bacteria etc. A number of methodologies using various catalyst and precursors are available for the preparation of pyrazine and quinoxaline. But many of them are associated with the major drawbacks. So, there is always a need to developea new and acceptable methodology for them.

Section B: Chapter IV (section B) deals with the preparation of pyrazine and quinoxaline derivatives form diverse precursor using 3, 5 Di-nitrobenzoic acid derived Copper (II) Complex

as a potent catalyst under mild reaction condition. We used different 1, 2- diketones and alkyl *vic*-diamine as pyrazine's precursor. In our primary attempt we choose benzil both substituted or unsubstituted/α-hydroxy ketone (1 mmol), *vic*-diamine/2-methyl *vic*-diamine (1 mmol), Cu (II)-catalyst (5 mol %) and methanol (3 ml) at 50^0 C. In our 2^{nd} attempt we replaced one or both the aromatic ring of benzil with H or other alkyl group and do the reaction under same reaction condition. Then we choose electron withdrawing substituent for the *vic*-diamine. We used 2, 3-diaminomaleonitrile as our *vic*-diamine source and continued our reaction at the optimized reaction condition. In all the cases we get good to excellent yield of desired product, i.e. pyrazine derivative. Then we check the activity of catalyst for quinoxaline preparation. We choose 1, 2-di ketone (1 mmol), o- phenylene diamine (1 mmol), Cu (II)-catalyst (2.5 mol %) and methanol (3 mL) at 40^0 C for preparation of 2, 3-disubstituted quinoxaline. After getting satisfactory result we choose phenacyl bromide (substituted/unsubstituted) as another precursor for quinoxaline synthesis. We find phenacyl bromide (1 mmol), o- phenylene diamine (1 mmol), copper catalyst (10 mol %), Na_2CO_3 (1 equiv.) and methanol (3 mL) at refluxed condition, as our optimized reaction condition. We check the applicability of the protocol against some substituted phenacyl bromide/ o- phenylene diamine. We get expected result for all the cases.

Section C: Chapter IV (section C) deals with the preparation of 2, 3-disubstituted quinoxaline from an unconventional but easily available precursor. To omit the drawbacks related to the conventional precursor we used 2-idobenzoic acid as our precursor. In this investigation we took benzil (1mmol), 2-iodobenzoic acid (1mmol), Cu (II)-catalyst (10 mol %), NH_4OH (1 mol %) and NaN_3 (1 mmol) in DMSO (3 mL) under reflux condition for our reaction. We got good to moderate yield of required product during our reaction. Diketones with low boiling points give poor yield during the reaction.

Preface

High significance, wide scope and multipurpose uses of C-hetero bonds inspire the author to carry out the methodological reaction-based work on C-hetero bond forming reactions. Carbon-hetero bond has a distinct position in organic chemistry in concern of their medicinal or material properties. Most of the pharmaceuticals are often contains Carbon-nitrogen bonds whereas basically all of the natural products contain Carbon-oxygen bonds. Besides, heterocyclic compounds which have C-S, C-O or C-N bonds are found in all application of biochemistry/chemistry. Extensive research work has been done to explore or to find the biological importance as well as material properties of these classes of compounds by several research groups.

The area of Carbon-heteroatom bond forming reactions has gained a mammothattraction due to the wide range of applications they have in designing the compound withchemical or biological activities. Thus, extensive amount of new methodologies has been developed for their synthesis. Most of thereported methodological works doesn't fit well in aspect of their easy, straight-forward or environmentallybenign nature. Thus, development of new methodologies is still going on to reach the green andmild approach for the sustainable development. Among the varieties ofcarbon-hetero compounds, this thesis covered methodological based works on some ofthem. This thesis contains the conversion of aldehyde into nitrile catalysed by Fe_3O_4-CTAB nano particle, polymeric Cu (II)-catalysed simple and mild transformation of diketone into 2, 3, 5-trisubstituted imidazole, preparation of pyrazines and quinoxalines derivatives form the conventional precursors by mild reaction technique using the same polymeric Cu (II)-catalyst and finally the preparation of quinoxalines form an unconventional predecessor.

The key aim of this thesis is to offer new literature on methodological work on C-heteroatom bond basically carbon-nitrogen forming reactions. The new methodological protocols described in this thesis are cost-effective, milder and environment friendly which definitely meet the presentdemand on the aspect of green and sustainable development.

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Appendix A

List of Published/Communicated Papers

1. Fe_3O_4-nanoparticles catalyzed an efficient synthesis of nitriles fromaldehydes, Pranab Ghosh, **Bittu Saha**, Gyan Chandra Pariyar, Abiral Tamangb, Raju Subba, *Tetrahedron Letters, 57,* **2016**, 3618-3621.
2. 2-Iodo benzoic acid: an unconventional precursor for the one pot multi-component synthesis of Quinoxaline using organo Cu (II) catalyst, **Bittu Saha**, Bijeta Mitra, Dhiraj Brahmin, Biswajit Sinha, Pranab Ghosh, *Tetrahedron Letters, 59,* **2018**, 3657-3663
3. $FeCl_3$-silica: A Green Approach for the Synthesis of Nitriles from Oximes- Pranab Ghosh, Gyan Chandra Pariyar, **Bittu Saha** and Raju Subba, *Synthetic Communication, 46*, **2016**, 685-691.
4. 3, 5 – Di-nitrobenzoic Acid Derived Copper II Complex Catalysed One pot multi components Synthesis of 2, 4, 5-trisubstituted Imidazoles Under solvent free conditions- **Bittu Saha**, Pranab Ghosh, Raju Subba, Dhiraj Bhraman, Rabindranath Singha, Biswajit Sinha and Abiral Tamang, Communicated to *Synthetic communication*, Manuscript ID LSYC-2018-12206.
5. Use of Cu (II) catalyst: an efficient synthesis of substituted N-heterocycles via double condensation/ tandem oxidation-cyclisation/elimination-cyclisation reactions from easily accessible precursors, Bittu Saha, Bijeta Mitra, Raju Subba, Dhiraj Bhraman, Biswajit Sinha and Pranab Ghosh. Communicated to *Tetrahedron Letters*, manuscript number: TETL-D-18-02113.
6. Selenium Dioxide Oxidation of Oxime derivative of Lupanone and Antimicrobial activity of the Oxidized Products, Ashim Ghosh, **Bittu Saha**, Bhim Prasad Pradhan, Pranab Ghosh, *Res. J.Chem.Sci*., *3(10)*, **2013**, 64-68.
7. Phytochemical investigation of the toluene extract of the root of *Croton bonplandianum* Bail, Ashim Ghosh, **Bittu Saha**, Jayanta Das and Pranab Ghosh, *Natural Product-An Indian Journal, 10(5),* **2014**,153-158.
8. Triterpenoids from Gynocardia odorata of Darjeeling foothills and their antimicrobial activity, Pranab Ghosh, Ashim Ghosh, Prasanta Chakraborty and **Bittu Saha**, *Jr. Indian Chem. Soc*., *91*, **2014**, 309-12.

Appendix B

List of research papers presented in the preceding seminars

1. Catalytic role of 3, 5-diitrobenzoic acid derived copper (II) complex for the synthesis of substituted quinoxaline and benzimidazole on silica, **Bittu Saha**, Raju Subba, Dhiraj Brahmin, Gayan Chandra Pariyar, Bijeta Mitra, Rabindranath Singha, Biswajit Sinha, and Pranab Ghosh. *- 19th CRSI National Symposium in Chemistry (14-16 July)-Organized by Department of Chemistry, University of North Bengal, Darjeeling- (Poster Presentation).

2. Poly [(μ_3-3,5-dinitrobenzoatok^3 O^1:O$^{1'}$:O^3) (μ2-hydroxido-k^{2}O:O)-copper(II)]- a robust catalyst for 2 , 4, 5-trisubstituted imidazole synthesis under solvent free condition, **Bittu Saha** and Pranab Ghosh. *- National Seminar on "Frontier in Chemistry 2017-18", (14th Sept, 2017) organized by Department of Chemistry, University of North Bengal, Darjeeling. (Poster Presentation).

Appendix C

Abbreviations

$CHCl_3$	Chloroform	PTFE	Polytetrafluoroethylene
Al_2O_3	Aluminium oxide	$NaHCO_3$	Sodium bicarbonate
$(NH4)_2S$	Ammonium sulfide	TMS	Tetramethyl silane
DMSO	Dimethyl sulfoxide	TMDS	1, 1, 3, 3-tetramethyldisiloxane
NH_4OH	Ammonium hydroxide	NaCN	Sodium cyanide
NH_4OAc	Ammonium acetate	$Ru_3(CO)_{12}$	Triruthenium dodecacarbonyl
TfOH	Triflic acid	KCN	Potassium cyanide
KOH	Potassium hydroxide	HCl	Hydrochloric acid
MeOH	Methanol	KI	Potassium iodide
CuI	Cuprous iodide	Na_2SO_4	Sodium sulphate
NBS	N-bromosuccinimide	$PhCF_3$	Trifluoro toluene
$CuSO_4,5H_2O$	Copper (II) sulphate	Fe_3O_4	Iron oxide
CH_3CN	Acetonitrile	P_2O_5	Phosphorus pentoxide
$Cu(BF_4)_2$	Copper (II) tetrafluoroborate	DCE	Dichloroethane
CuCN	Cuprous cyanide	NH_4Cl	Ammonium chloride
K_2CO_3	Potassium carbonate	THF	Tetrahydrofuran
^tBuONO	tert-Butyl nitrite	NaH_2PO_4	sodium dihydrogen phosphate
KBr	Potassium bromide	Na_2CO_3	Sodium carbonate
DMF	N, N-Dimethylformamide	$Cu(NO_3)_2$	Copper nitrate
$Zr(acac)_4$	Zirconium acetylacetonate	$NiCl_2$	Nickel chloride

Et_3N	Triethyl amine	$AgNO_3$	Silver nitrate
$FeCl_2$	Ferrous chloride	InF_3	Indium (III) fluoride
$FeSO_4.7H_2O$	Iron (II) sulphate heptahydrate	KNO_3	Potassium nitrate
Bi_2O_3	Bismuth (III) oxide	$Cu_2(OTf)_2$	Copper (I) triflate
$K_2S_2O_8$	Potassium persulfate	$NH_2OH.HCL$	Hydroxylamine hydrochloride
I_2	Iodine	$PhSiH_3$	Phenyl silane
Cs_2CO_3	Cesium carbonate	Na_2SO_4	Sodium sulphate
$NaNO_2$	Sodium nitrite	K_3PO_4	Potassium phosphate
OIPh	Iodosyl benzene	Pd	Palladium
H_2O_2	Hydrogen peroxide	NaN_3	Sodium azide
$ZnCl_2$	Zinc Chloride	PhMe	Toluene
$K_3[Fe(CN)_6]$	Potassium ferricyanide	Me_3SiN_3	Trimethyl silyl azide
$CuBr_2$	Copper (II) bromide	MoO_3	Molybdenum oxide
H_2SO_4	Sulfuric acid	WO_3	Tungsten trioxide
$(NH_4)_2SO_4$	Ammonium sulphate	NH_4F	Ammonium fluoride
$(NH_4)_2CO_3$	Ammonium carbonate	NH_4HCO_3	Ammonium bicarbonate
NH_4HF_2	Ammonium bifluoride	$(NH_4)_2HPO_4$	Diammonium phosphate
NH_4SCN	Ammonium thiocyanate	HCO_2NH_4	Ammonium acetate
$FeCl_3$	Ferric chloride	MnO_2	Manganese dioxide
CuO	Copper (II) oxide	ZnO	Zinc oxide
SiO_2	Silicon dioxide	CAN	Ceric ammonium nitrate
$MnFe_2O_4$	Manganese ferrite	$Cu(OTf)_2$	Copper (II) triflate
$Ga(ClO_4)_3$	Gallium (III) perchlorate	CuCl	Cupper (I) chloride

mmol	Millimole	mL	Milliliters
^{o}C	Degree Celsius	h	Hour
Min	Minute	ppm	Parts per million
m.p	Melting point	Temp	Temperature

TCBDA	*N*, *N*, *N*′, *N*′-tetrachlorobenzene-1, 3 disulfonamide
PCBS	*N*, *N*′-dichloro-*N*-ethylbenzene-1, 3- disulfonamide
TEA	Triethyl amine
Ac_2O	Acetic anhydride
DDQ	2, 3-Dichloro-5, 6-dicyano-1, 4-benzoquinone
PIDA	Phenyl iodine diacetate
TBAB	Tetrabutylammonium bromide
TEMPO	2, 2, 6, 6-Tetramethylpiperidine 1-oxyl
DABCO	1, 4-diazabicyclo [2, 2, 2] octane
Bpy	2, 2'-bipyridine
TBAF	Tetra-butyl ammonium fluoride
AcOH	Acetic acid
MNPs	Magnetic nanoparticles
NHC	N-heterocyclic carbene
NHPI	N-Hydroxy phthalimide
SBA-15	Mesoporous silica
TFE	Tetrafluoro ethylene
TFA	Trifluoro acetic acid

DOPA	3, 4-dihydroxy phenylalanine
CTAB	Cetyltrimethylammonium bromide
PEG	Polyethylene glycol
GO	Graphene oxide
XRD	X-ray diffraction
SEM	Scanning electron microscope
TEM	Transmission electron microscope
AAS	Atomic Absorption Spectroscopy
FT-IR	Fourier transform infrared spectroscopy
NMR	Nuclear magnetic resonance
TLC	Thin layer chromatography
TMEDA	Tetra methyl ethylene diamine

CHAPTER-I

(General Introduction)

I. 1. A brief Introduction of C-hetero Bond:

Molecules containing heteroatoms, such as nitrogen, oxygen and sulphur, which are holds by C-hetero bonds, acts as most imperative subtype of organic molecules in the dominion of biomedical science and also in material sciences.For example, apt derivatives of C-hetero molecules act as important fragments for many natural as well as synthetic drugs to heal diseases, ligand modeling for transition metal complexes in both biological and non-biological system, non-classical isosteres for the carboxylic acid moietyof biologically active molecules, fluorescent dyes for biological labelling, plant growth regulators in agriculture, intermediates for organic synthesis and also as protector for many functional groups. Besides, C-heteroatomscontaining compounds, also shows catalytic activity for organic transformations (e.g. tert-butyl ammonium bromide, acts as phase transfer catalyst/enzymes for cellular reactions). Therefore, these groups of compounds attain an immense importance for their momentous properties in spacious area of research and also C-hetero bond formation reactions have occupied a unique site in organic chemistry from decades.

I.2. Objectives and scope of the thesis:

C-hetero bond forming reactions by an economical and environmentally friendly process is always desirable for paramount interest of heterocyclic compounds in medicinal (for both pharmaceutical and drug design) industries. It provides direct, step- and atom-economical approaches towards heterocycles containing C-N/C-O/C-S bonds such as amides; aza/oxo/thio-heterocycles etc. (which provides basic structural units or skeletons for construction of biologically as well as pharmaceutically active compounds/drugs). Besides, employing privileged scaffolds for combinational synthesis by C-hetero bond forming reactions, seemingly exploited the positive screening results for libraries of active compounds. Its positive impact can be seen on society as human healthcare, advanced technology for everyday life e.g. food, antibiotics, perfumes etc. and also in the field of research itself.

Hence, substantialamount of methodologies has been established for their synthesis. Among accustomed methods for C-hetero bond forming reactions,except very few protocols (which are effective under relatively milder condition compared to others),most comprised with-high cost of some metal salt, need hazardous solvent or specially designed catalysed, using of additives, forming non-disposal side products and abnormally high reaction time etc., restrict their practical utility for large-scale process. Thus, the advent of new and specific method for C-heteroatom bond forming reactions makes us alert to investigate the present topic.

Between the plenteous of compoundshaving carbon-heteroatom, the present methodological based work embodied in this thesis is especially focused on some nitrogen containing hetero moiety.The thesis is covered with synthesis of nitrile from aldehyde using Fe_3O_4 nano particle, preparation of highly substituted imidazole and also preparation of substituted pyrazine/ quinoxaline from conventional/ unconventional precursor using reaction catalysed by an polymeric Cu (II)-catalyst. The major aim to carry out the present methodological work of this thesis is to provide mild, cost-effectiveand environment friendlyprotocol for the synthesisof useful compounds containing especially C-N bond by carbon-hetero bond forming reactions.

I.3. Brief review of the compounds described in this thesis:

I.3.1. Biological profile of compounds having carbon-Nitrogen bonds:

Suitably design organo-hetero atomic molecules are widely recognized as biologically attractive molecules. Likewise, organo-nitrile functionality stretches an important structural feature towards the naturally occurring or synthetic biological potent moiety. For example, in (fig I.1) Gallopamil (a L-type calcium channel blocker and also useful for treatment for cardiac arrhythmias), Alogliptin (an anti-diabetic drug of DPP inhibitor class), Nilvadipine (used for treatment of hypertension), Febuxostat (used in treatment for hyperuricemia and chronic gout).

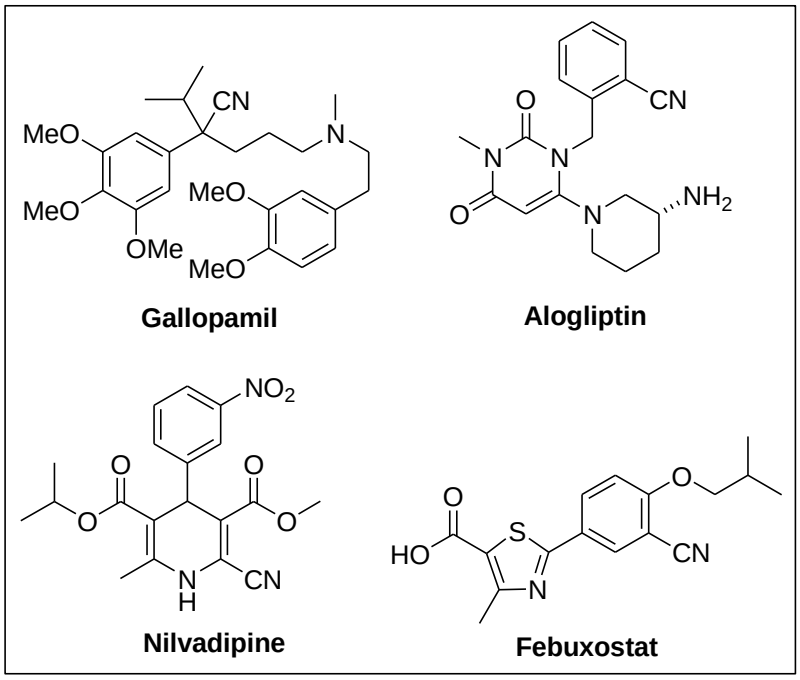


Fig. I. 1. Some biologically active nitrile containing molecules

Nitrogen containing heterocycles prevailed attraction in present era according to their inhibitory effect and promising selectivity ratio towards pharmaceuticals and active chemical intermediacy. Extensive studies have shown that these classes of moiety have prominent medicinal values against numerous strain microorganisms. Among the widely spread C-N containing heterocyclic scaffold, imidazole and its derivatives are incorporated with generous biological activities (e.g. Histidine, an important amino acid, serving as basic framework for many enzymes/proteins and also plays a vital role for Hemoglobin, has an imidazole side-chain).Besides,hydrogen bond donor- acceptor capabilities [1]equip imidazole pharmacophore anadditional therapeutic effect towards systemic fungalinfections[2],amphiphilic molecule for drug delivery[3]and also for treatment of many parasitic decreases (Fig. I. 2)[4].

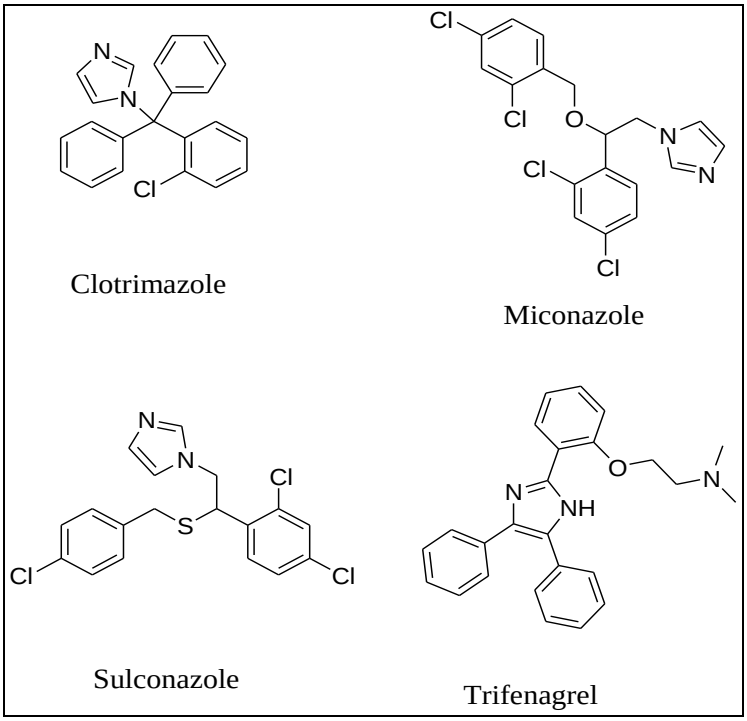


Fig. I. 2. Some biologically potent imidazole drugs

Other privilege fragments of N-heterocyclic modules those are highly abundant in many biologically important compounds, are pyrazine and quinoxalines. Among them Pyrazine and its derivatives are important components of aromas for various vegetables, wines and fruits etc. and also present as a basic moiety of some biological potent molecules (e.g.Folic acid, has pyrazine ring fused with pyrimidine ring in its basic skeleton; fig. I. 3).

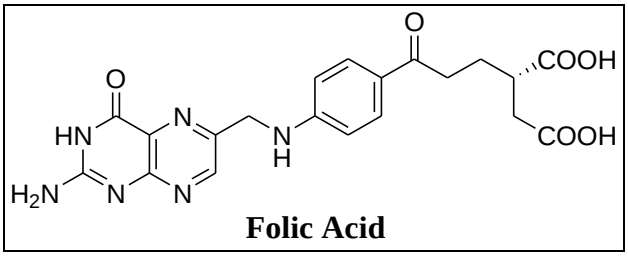


Fig. I. 3. Folic acid

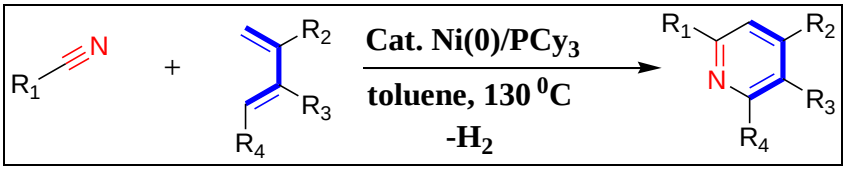
Again, they show profound effectas relaxing agent for cardiovascular and uterine smooth muscle[5], cyclooxygenase enzyme (COX-2) inhibitor[6], antithrombotic agents[7], analgesic effects[8], anti-platelet aggregationactivity [9], inhibitor of various protein kinase [10]/leukotriene production [11] and also used for treatment of neurodegenerative disorder [12]/ bone related disorder [13].Moreover,appropriate pyrazine derivatives can decrease nitric oxide production in human body[14]. Along pyrazines, quinoxalines derivatives are also regarded as an auspicious class of bioactive nitrogenous-heterocyclic compounds that exhibit wide range of biologicalactivities (e.g. many quinoxalines-basedantibiotics are used for inhibiting the growth of transplantable tumors[15] and also for Gram-positive bacteria[16]).

I.3.2. Application of C-N hetero compounds towards organic transformative reaction prospect:

I.3.2.1. Role of nitriles in organic transformations:

From long-time the applicability of nitriles towards the organic transformation are well established. They can easily transformed into amines (e.g. conversion of alkyl nitriles to corresponding tertiary/secondary alkyl amines using a source of dihydrogen and catalysed by heterogeneous palladium catalyst in aprotic solvents[17]),carboxylic acids (e.g. recyclable [bmim]HSO_4ionic liquid catalysed formation of carboxylic acid from their respective nitriles[18]), amides (transformation of aliphatic/aromatic nitriles to their corresponding amides by selective hydration using Ru (II)-phosphaurotropine[19]), aldehydes (e.g.1, 1, 3, 3-tetramethyldisiloxane (TMDS)/triisopropoxyvanadium(V) oxide catalysed chemoselective reduction of nitriles to aldehydes[20]),amidines (e.g. ytterbium catalysed addition of nitriles with amines to form monosubstituted N-aryl amidines[21], esters[22]),1,2-diketones[23]and also serve as prominent intermediate for the construction of other bioactive nitrogenous heterocyclic compounds such as pyrimidine[24], pyridine (e.g., water soluble cobalt(I) catalysed cyclotrimerization of one mole nitrile with two moles of alkynes to get highly functionalized pyridines[25]or Ni(0)-catalyzed intermolecular dehydrogenative [4 + 2] cycloaddition reaction of 1, 3-butadienes with nitriles for synthesis of pyridine derivatives;schemeI.1[26]) and pyrrolidines (e.g., 2-sustituted pyrrolidines preparation from commercially available nitriles[27]),derivatives. Besides, literature also reveals the usage of nitriles for- production of substituted oxazole[28], thiadiazol (e.g., $(NH_4)_2S$ and 2, 4, 6-trichloro-1, 3, 5-triazine promoted synthesis of 3, 5-diaryl-1, 2, 4-thiadiazoles in 1-butyl-3-

methylimidazolium bromide)[29],single-step synthesis for 5-substituted-1*H*-tetrazole through cycloaddition reaction (e.g., [1, 3]-dipolar cycloaddition reactions of boron-azides and nitriles for 5-substituted 1*H*-tetrazoles[30]), tetrazole-tethered *C*-glycosyl α-amino acids[31] and also for single step formation of amide from alcohol/amide using ruthenium as a catalyst [32].



Scheme. I. 1. Formation of substituted pyridines

I.3.2.2. Use of nitrile groups for the preparation of ionic liquid:

Nitrile functionalization to an ionic liquid drastically changes the physiochemical properties of it. Recently, Youquan Deng et. al. has reported the same observation by incorporation of CN group to imidazolium, pyridinium and quaternary ammonium based ionic liquids [33]. Besides, nitrile functionalized ionic liquids can providea good alternative towards many reactions (e.g. Dyson et. al has reported the application of pyridinium ion with nitrile functionalization ionic liquids inSuzuki and StilleC-Ccoupling reactions[34]).Again, Dyson et. al. reported a nitrile functionalized pyrrolidinium ionic liquid and implemented it as a solvent for cross coupling reaction [35].

I.3.2.3. Application of imidazoles in organic transformations:

Imidazole,as a moiety is associated with many biologically as well physiologically active natural and synthetic organic compounds.Besides, the presence of twonitrogen atom, makes imidazole moieties to serve as ligand to manytransition metals complexes and also used as organo-catalyst for extensive organic transformations. In recent days imidazole also assists as a useful organic counterpart for ionic liquids preparation.

I.3.2.3.1. Role of imidazole derivatives in organic ligands:

Versatality in bonding modes of nitrogen gives imidazoles/substituted imidazoles to plays an imperative role in development of transition metal coordination chemistry. Recently imidazole derivatives are servingas a convenient ligand for substantial number oftransition metals (e.g.,

imidazole-based chiral biaryl P, N-ligand; Fig. I.4 has prepared and implemented by Aaron Aponick et al., shown exceptionally well enantioselectivity during the asymmetric coupling reaction[36].

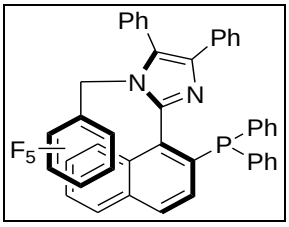
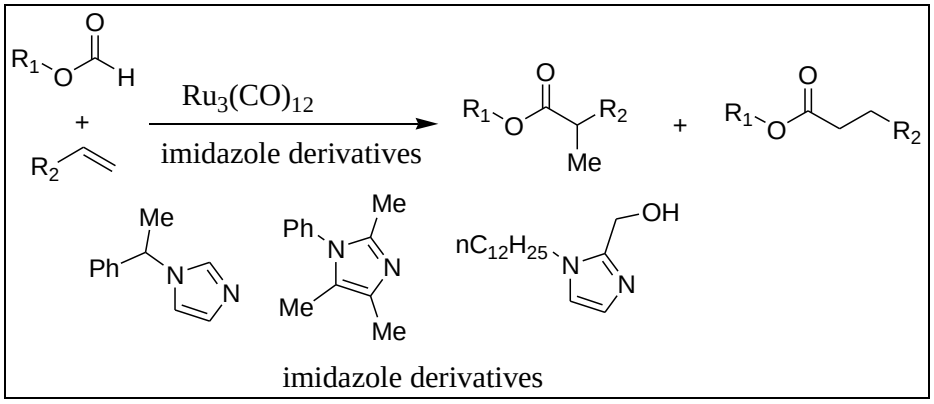


Fig. I. 4. Imidazole based chiral ligand.

Besides, Kei Manabe et al. used imidazole derivatives (scheme. I. 2) as a useful ligand for Ru-catalyzed hydro-esterification to afford 1-carbon elongated esters in high yields[37].



Scheme I. 2. Imidazole derivatives as ligand

Roman Sívek, Filip Bureš et al. also reported the application of imidazole based potential bi/tri-dentate ligand in asymmetric synthesis[38].Recently imidazole-based N-heterocyclic carbenes are also used as profound ligand for many organo transition metal and catalysed coupling reactions (e.g. 2nd generation Grubbs catalyst [39]).

I.3.2.3.2. Use of imidazole for the preparation of ionic liquids:

In recent years room temperature ionic liquids have gained immense interest as an alternative to the conventional hazardous organic solvent. Also, for many reactions they play important catalytic role. Furthermore, combination of different alkyl-substituent and counter ions enables to regulate the properties of ionic liquid to satisfy the demand of application. Likewise,

imidazole derivative based ionic liquids have numerous applications including- serves as potential alternatives greener solvent for conventional organic solvents for their lack of volatility and also as water treatment agents for their co-ordination ability to metal ions. 1-Ethyl-3-methylimidazoliumchloride (Fig. I. 5) was the first synthesized imidazole based ionic liquid.

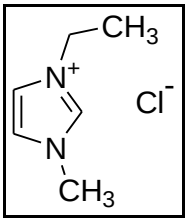
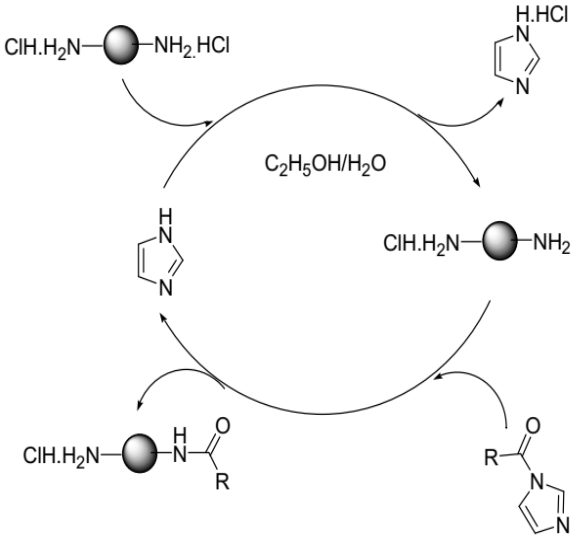


Fig. I. 5. 1-ethyl-3-methylimidazolium chloride

Later, exchange of chloride with more hydrolytically stable anions like SO_4^{2-}, BF_4^-, NO_3^- etc. make the ionic liquid quite stable.

I.3.2.3.3. Role of imidazoles and its derivatives in catalysis:

In modern daysImidazole/imidazole tuned with transition metal used as effective catalyst for numerous organic transformations (e.g. M. P. Kaushik et al. have recently reported selectivemonoacylation of symmetrical primary and secondary aliphatic diamine using imidazole as a catalyst; scheme. I. 3) [40].



Scheme. I. 3. Mono acylation catalysed by imidazole

Also, Marc L. Snapper et al. reported an enantioselective silylation of racemic diols to access enantiomerically enriched monosilylated regioisomers catalysed by an amino acid-based imidazole catalyst[41]. Moreover, self-assembled poly(imidazole-palladium) synthesized by Yasuhiro Uozumi et al., can acts as a highly active and reusable catalyst for theallylic aryl/alkenylation of allylic acetates/carbonates with arylboronic acid, tetra aryl borates,and alkenyl boron in water/alcohol medium[42]. Also, the same group has reported the effectual activity of the solid phase catalyst (self-assembled $CuSO_4$and a poly-(imidazole-acrylamide) amphiphile), towards the Huisgen [1, 3]-dipolar cycloaddition reaction and also for three component cyclization of organic halides, alkynes and sodium azides[43]. Recently P.R Bhagat et al have reported the use of imidazole based NHC-cabene-Pd complex for MizoRoki- Heck reaction[44].

I. 3.3. Other applications of C-N bonds containing compounds:

I.3.3.1. some industrial/domestic applications of nitriles:

Besides the applicability as a biologically potent functional group and intermediacy for many organic moleculesyntheses, nitriles are also found in many industrially useful compounds. Such as nitrile rubber (Fig. I. 6.) also known as Nitrile-butadiene rubber (NBR)is a highly resistant synthetic polymeric rubber towards oil, fuel and other chemicals, makes it more prior than the ordinary rubber to make hoses during handling oil and fuel, grommets and seals in aeronautical and automotive industries and also used to make protective gloves for nuclear industries. Along with it, the resiliency of NBR, makes it's a useful ingredient for making disposable lab, examination and cleaning gloves. Besides,NBR are also used to create footwear, latex-free gloves, floor mats, automotive transmission belts, O-rings, sponges and expanded foams etc.

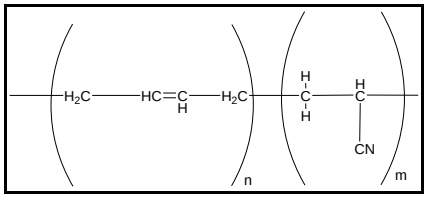


Fig. I. 6. General structure of nitrile rubber

Ethyl cyanoacrylate is (fig. I.7.) a nitrile based derivative acts as basic component for cyanoacrylate glues in industry.

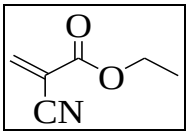


Fig. I. 7. Ethyl cyanoacrylate

Moreover, aromatic nitriles are used to prepared liquid crystal (e.g., 4-Cyano-4´-pentylbiphenyl, an aromatic cyano-derivative typically used to make liquid crystal; fig. I. 8.), as well as for various dyes.

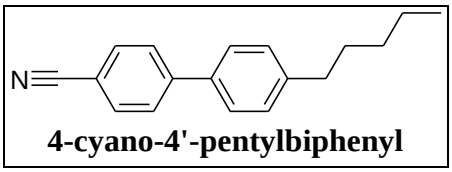


Fig. I. 8. 4-Cyano-4´-pentylbi phenyl

I.3.3.2. Uses of Imidazole, pyrazines and quinoxalines:

I.3.3.2.1. Industrial uses of Imidazole:

Industrially imidazoles are used as a corrosion inhibitor especially for copper metal to maintain its conductivity especially in aqueous medium where it may decrease due to corrosion of copper. Another important imidazole derivative thermostable polybenzimidazole contains imidazole (also fused and linked with benzene ring), is acts as a fire retardant. Besides, numerous compounds of imidazole are used as photosensitive agent in photography[45], cryogels for removing heavy metals[46] and also some of them are used in chemiluminescence system[47].

I.3.3.2.2. Industrial uses of Quinoxaline:

Like nitriles and imidazoles, quinoxalines have also industrial importance. Suitable quinoxaline derivatives are (e.g. acenaptho [1,2b] quinoxaline; Fig. I. 9.)[48] regarded as corrosion inhibitor of mild steel in acidic condition. Moreover, for structural similarities to natural chromophorequinoxalines are used to prepared porphyrins and also for the electroluminescent materials.

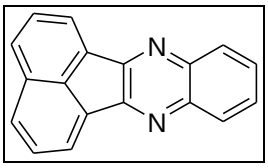


Fig. I. 9. Acenaptho [1,2b] Quinoxaline

I.3.3.2.3. Industrial uses of pyrazines:

Like other N-heterocyclic compounds, pyrazine and its derivatives are also having their own industrial importance. For their overwhelming flavor profile ranging from sweet to savory, make them imperative ingredient in Flavor and fragrance industries. Pyrazine derivatives such as, alkyl pyrazine (e.g. 2,3-dimethyl pyrazine/2,3,5trimethyl pyrazine; Fig. I. 10.) and alkoxy pyrazine (e.g. 2-Ethoxy pyrazine/6-methoxypyrazin-2-amine; Fig.I.10.) havecharacteristic nutty/chocolate olfactive and perfectly used in candies or bakery's industries.

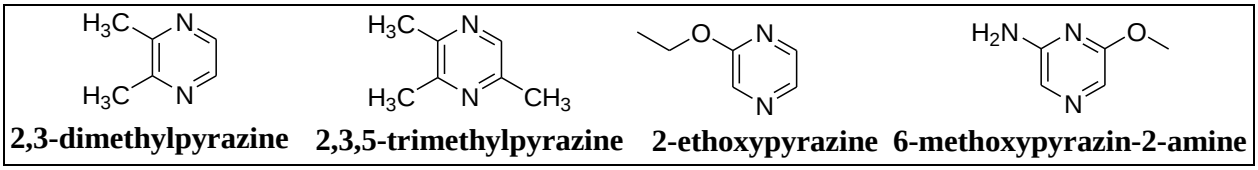


Fig. I. 10. Alkyl and alkoxy derivatives of pyrazine

I.4.Conclusion:

Compounds having carbon-hetero bonds have a broad scope in the area of designing the molecules with a chemical, biological or pharmaceutical interest. Most of the pharmaceuticals are covered by the compounds having carbon-hetero bonds. The bioactive natural products include carbon-heteroatom bond in their functional site. Therefore, molecules having carbon-hetero bond would be the suitable intermediates for natural product synthesis. Chemically interesting suitable molecules having bi or multifunctional system would perform efficient ligands for the complicated organic transformations. Carbon-hetero bond can be more easily functionalize than carbon-carbonnon-polar olefinic bond. Thus, functional groups inter-conversion, preparation of bi-or multifunctional compounds can be easily carrying out by applying suitable reagents to

carbon-hetero bond. With these huge importance and broad scope of carbon-hetero bond, author felt necessary to find a mild and easiest route for the synthesis of such type of important organic intermediate under mild, easy and straightforward approach.

Chapter II

Fe_3O_4-nanoparticles catalyzed an efficient synthesis of nitriles from aldehydes

Section A

(A general introduction of nitrile and its synthetic background)

II. A. Nitrile:

An organic compound with -CN functional group is considered as nitrile whereas for inorganic compounds they are known as cyanide. Besides, any organic compound contains many -CN group are known as cyanocarbon in industrial literature. Applicability of these function group is well documented and we already discussed it in our general introduction section (chapter I) of this thesis. Here we only discussed about the structure, occurrence and some sort of synthetic background of the functional group.

II. A. 1. Discovery of organo nitriles:

In 1972, C. W. Scheele was the first, who prepared hydrogen cyanide and nitrile of formic acid. Later on, J. L. Gay-Lussacin 1811 prepared the very toxic and pure acid. Friedrich Wöhler and Justus von Leibig, first prepared the nitrile of benzoic acids but was unable to examined the physical or chemical properties, for the low yield of the product. In 1834, Théophile-Jules Pelouze has synthesized propionitrile and suggesting it as the ether of propionic alcohol and hydrocyanicacid. In 1844 Hermann Fehling discovered a method (by heating ammonium benzoate), to get sufficient benzonitrile for chemical research. Hermann Fehling devised the name nitrile, for the newly found substance and became the name for this group of compounds.

II. A. 2. Structure of -CN group:

sp-Hybridization of the triple bonded C of -CN, give it a linear skeleton with a bond distance around 1.16^{0} A. Also, electronegetivity differences between nitrogen and carbon make it a polar group with high dipole moment.

II. A. 3. Natural occurrences of nitrile:

Naturally, organo-nitriles are found in some plants, certain seeds and fruit stones (e.g., those of apples, peaches and apricots etc.) and also produced by some fungi, bacteria and algae. In plants, -CN groups are present as cyanogenic glycosides (an amygdalin skeleton; Fig. II. A.1.); in which they are attached with a sugar moietie and helping to protect plants from herbivores. In tropical countries a potato-like food, Cassava roots has grown (also named manioc; used to make tapioca), also contain cyanogenic glycosides.

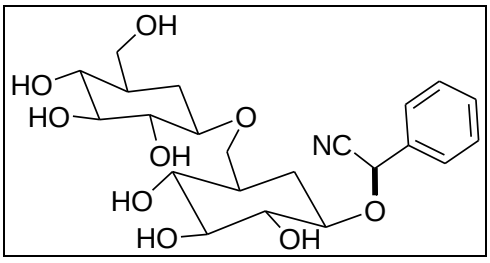
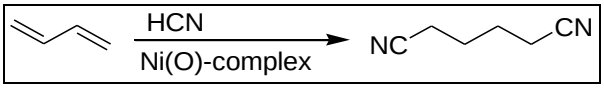


Fig. II. A. 1. Cyanogenic glycosides

II. A. 4. Classical method for nitrile synthesis:

II. A. 4. 1. Hydrocyanation:

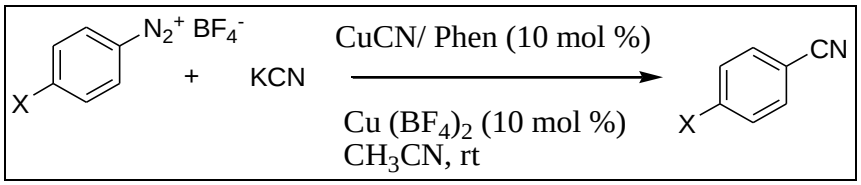
Hydrocyanation [1] is the industrial process of formation of nitrile using an alkene and hydrogen cyanide. The process involves a thermodynamically favorable H^+ and CN^- addition to an activated C=C, such as C=C bond of α, β-unsaturated carbonyl compound. For this process sufficiently activated substrates are required thus inactivated alkenes were unfavorable for this reaction. But this is conquered by transition-metal catalysis. By, using transition-metal catalyst addition of CN^- across π-bonds occurs in a Markovnikov/anti-Markovnikov fashion to provide fully saturated nitriles. The most commonly used transition-metal complexes for the purpose is nickel (0) and palladium (0) complexes. For industrial purposes the reaction is widely used in preparation for adiponitrile (NC-$(CH_2)_4$-CN); a predecessor for hexa-methylene diamine; from 1, 3-butadiene using Ni-complexes (scheme. II. A. 1.).



Scheme. II. A. 1. Modern process for adiponitrile synthesis

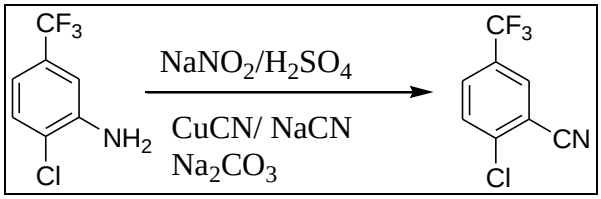
II. A. 4. 2. Sandmeyer reaction:

This method involves the direct cyanation of azobenzene using cuprous cyanide to get aryl nitrile. But the use of more toxic metal cyanide and less selectivity results the process less useful industrially. Recently P. Beletskaya et al. have reported the catalytic version of Sandmeyer reaction using Cu(I)/ Cu (II) catalyst (scheme. II. A. 2.)[2].



Scheme. II. A. 2. Catalytic version of sandmeyer reaction

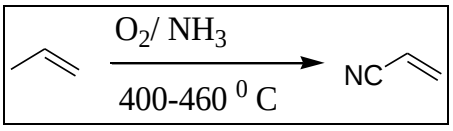
Now, industrially the reaction is used to synthesis a key intermediate for the anti-psychotic drug Fluanxol (scheme. II. A. 3)[3].



Scheme. II. A. 3. Synthesis of the key intermediate for Fluanxol

II. A. 4. 3. Ammoxidation reaction:

In ammoxidation [4] technique reaction of hydrocarbon is takes place with ammonia by the presence of oxygen and a suitable catalyst. Usually alkenes are used as the hydrocarbon source and partially oxidized by oxygen in presence of ammonia (e.g. preparation of acrylonitrile scheme. II. A. 4).

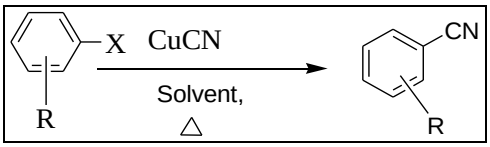


Scheme. II. A. 4. Preparation of acrylonitrile

Besides, derivatives of benzonitrile, iso-butyronitrile and phthalonitriles are also prepared by this method. The first acknowledge commercial plant on the basis of the reaction was built by Sohio (now BP international). They used Bi_2O_3/MoO_3 as their catalyst.

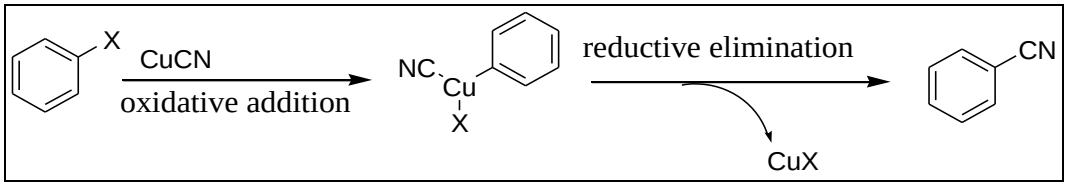
II. A. 4. 4. Rosenmund–von Braun reaction:

By this process aryl halides undergoes cyanation reaction with excess of Cu(I) cyanide in a polar organic solvent such as pyridine, DMF etc. under refluxing condition (scheme. II. A. 5).



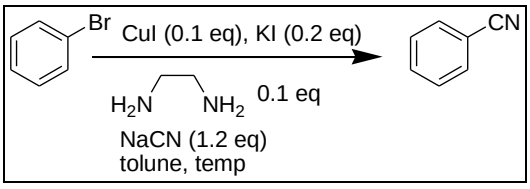
Scheme. II. A. 5. General reaction for Rosenmund-von Braun method

During the process it is assumed that the reaction takings through an oxidative addition of aryl halide to the copper cyanide and makes it Cu (III) species followed by reductive elimination to get the product (scheme. II. A. 6).



Scheme. II. A. 6. Mechanistic path-way for Rosenmund- von Braun reaction

The method was good for aryl iodide but it fails to satisfy for aryl bromides. Besides, it also has some other limitations regarding harsh reaction condition and also for separation of products from the copper halide side product. Most recently, S. A. Buchwald et al. have reported a modified technique for aryl-bromides (scheme. II. A. 7) [5]. They suggest a domino halide exchange-cyanation during the reaction.

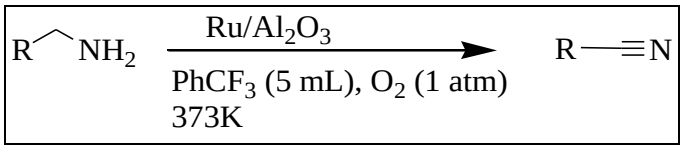


Scheme. II. A. 7. S. A. Buchwald method for aryl bromides transformation into nitrile

II. A. 5. Modern methods for synthesis of nitriles:

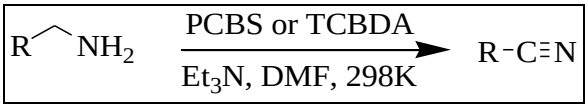
II. A. 5. 1. Synthesis of nitriles from primary amines:

Primary amines can have converted into nitrile by partial oxidation using suitable oxidizing agent and catalyst. There are so many protocols are present for this transformation. Such as Noritaka Mizuno et al. have synthesized nitrile from their corresponding amines (both activate and non-activated) by direct oxidative process using Ru/Al_2O_3 (1.4 wt. % of Ru) as heterogenous catalyst, 1 atm dioxygen or air in $PhCF_3$ (trifluoro toluene) as a solvent (scheme. II. A. 8) [6].



Scheme. II. A. 8. Oxidative transformation of primary amines

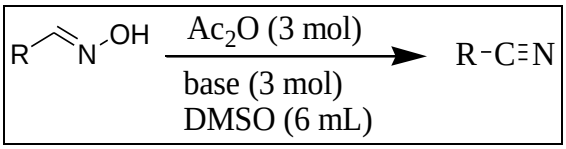
Again, another research group Ramin Ghorbani-Vaghei et al. recently transformed primary anime to their corresponding nitriles using *N*, *N*, *N′*, *N′*-tetrachlorobenzene-1, 3 disulfonamide (TCBDA) or poly (*N*, *N′*-dichloro-*N*-ethylbenzene-1, 3- disulfonamide) (PCBS), triethyl amine (TEA; acts as a base) and DMF (as a solvent) at 298 K temperature (scheme. II. A. 9) [7].



Scheme. II. A. 9. PCBS or TCBDA catalysed transformation of primary amine to nitriles.

II. A. 5. 2. Synthesis of nitriles from oximes:

Another alternative precursor for nitrile preparation is oxime. This process involves the dehydration of oximes to get their corresponding nitrile. Generally common dehydrating agent (such as conc. H_2SO_4 of P_2O_5) can used for the process but less selectivity of the reaction makes it inapplicable for industrial purpose. There are a number of alternatives are available such as, Guangyu Xu et al. used acetic anhydride as a dehydrating agent at weak alkaline condition (Scheme. II. A. 10). [8]

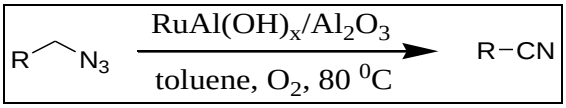


Scheme. II. A. 10. Conversion of oxime into nitrile

Again, Youquan Deng et al. convert aldoximes to their corresponding nitriles with the help of chlorosulfonic acid as a dehydrating agent in toluene [9]. Lei Yu et al. reported the precatalytic dehydration of aldoxime to nitrile using mild, tolerable and stable catalyst PhSe(O)OH [10].

II. A. 5. 3. Synthesis of nitrile from azide:

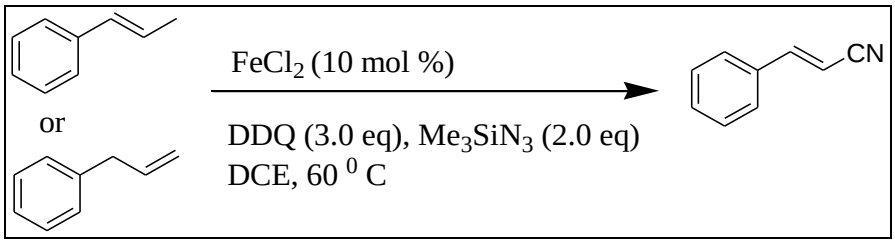
Another important method is the oxidative transformation of azides into nitriles. In 2005,Rozen et al. reported the direct conversion of organic azide into nitrile through BrF_3 promoted reaction without any incorporation of bromine or fluorine [11a]. Again, recently Noritaka Mizuno et al. have reported the transformation of primary azide into nitriles through an aerobic oxidation, using heterogenous ruthenium hydroxidecatalyst [$Ru(OH)x/Al_2O_3$] for their synthesis(scheme. II. A. 11)[11b].



Scheme. II. A. 11. Ru (OH)x/Al_2O_3 catalysed transformation of azide to nitrile.

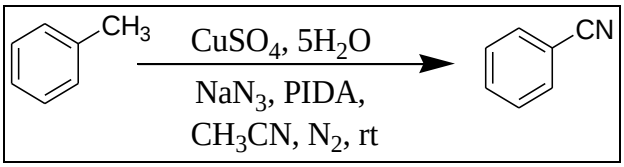
II. A. 5. 4. Synthesis of nitriles from benzyl or allyl halides, alkenes, methyl arenes and alkynes:

Direct transformation of benzyl/allyl halide, alkenes or methyl arenes by an elongation of one carbon to the parent precursor is also well known. Ning Jiao et al. have recently reported these transformations separately for halides, alkenes and methyl arenes. For alkene or allylarenes they used inexpensive iron catalyst using dry DCE (2 mL) as solvent to get the nitrile (scheme. II. A. 12). [12]



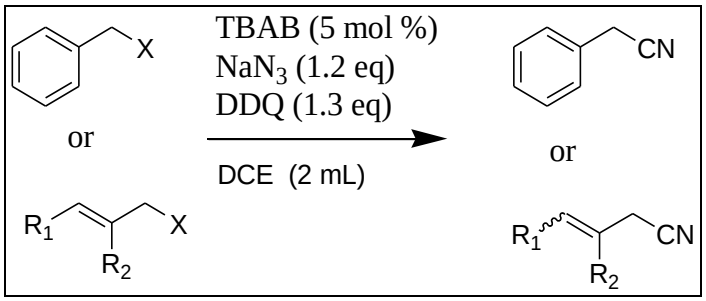
Scheme. II. A. 12. Conversion of alkene to nitrile

Again, for methyl arenes they have reported C(sp3)-H functionalization at room temperature using PIDA (1.6 mmol), NaN_3 (2.0 mmol) and $CuSO_4$,$5H_2O$ (0.25mmol) as a catalyst in acetonitrile under N_2 atmosphere (scheme. II. A. 13) [13].



Scheme. II. A. 13. C(sp3)-H functionalization for nitrile preparation.

Again, in continuation of their finding, they explore the direct conversion of benzyl/allyl halides to their respective nitriles by substitution and subsequent oxidative rearrangement (scheme. II. A. 14.) [14].



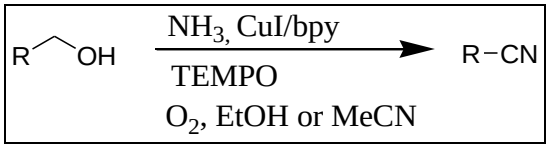
Scheme. II. A. 14. Conversion of benzyl/allyl halides to benzyl/ allyl nitriles

Recently D. Maiti et al. has reported the transformation of alkynes to their corresponding nitriles through a C≡C bond cleavage using *tert*-butyl nitrile as a reagent under metal free reaction condition (scheme. II. A.15) [15].

Scheme. II. A.15. Conversion of nitrile from alkynes

II. A. 5. 5. Synthesis of nitriles from alcohols acids and amides:

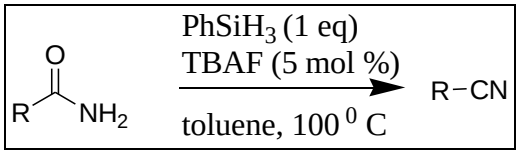
Recently Y. Haung et al. describe the aerobic double dehydrogenation reaction for the conversion of alcohol to nitrile CuI-bpy catalytic system and TEMPO under O_2 atmosphere. The process enabled a one pot transformation for various aromatic/aliphatic alcohols to nitriles (scheme. II. A. 16) [16].



Scheme. II. A. 16. CuI- bpy and TEMPO catalysed transformation of alcohols.

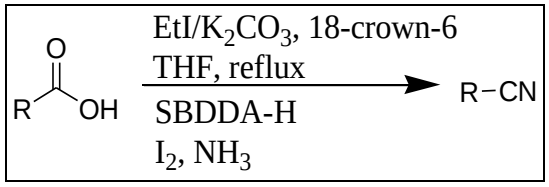
Again, J. M. Vatèle converts alcohols to nitrile through an in situ highly chemoselective oxidation-imination-aldimine oxidation reaction sequences using TEMPO, iodosobenzene diacetate and NH_4OAc [17]. This process serves well for a wide range of aliphatic/benzylic/hetero aromatic alcohols to give their respective nitrile in excellent yield.

Matthias Beller et al. reported the conversion of aliphatic and aromatic nitriles by catalytic dehydration of aromatic/aliphatic amides using silanes and catalytic amounts of tetra-butyl ammonium fluoride (TBAF) (scheme. II. A. 17) [18]. The protocol show higher selectivity under mild conditions.



Scheme. II. A. 17. Transformation of nitrile to amides

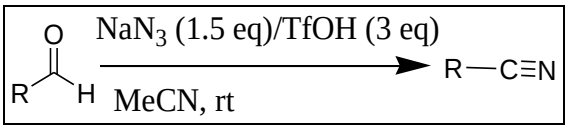
H. Togo et al. recently reported the treatment of organo acids with ethyl iodide/18-crown-6/ K_2CO_3 followed by treatment with SDDBA-H and finally with molecular iodine in aqueous ammonia converts it into corresponding nitriles (scheme. II. A. 18) [19].



Scheme. II. A. 18. Conversion of acids to nitriles

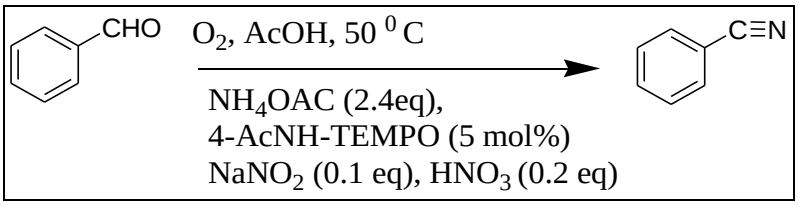
II. A. 5. 6. Synthesis of nitriles from aldehydes:

Aldehydes can easily have converted into nitriles through Schmidt type reaction as reported by J. R. Prabhu et al. (scheme. II. A. 19) [20] via in situ formation of hydrazoic acid by treatment of sodium azide with triflic acid (Tf OH).



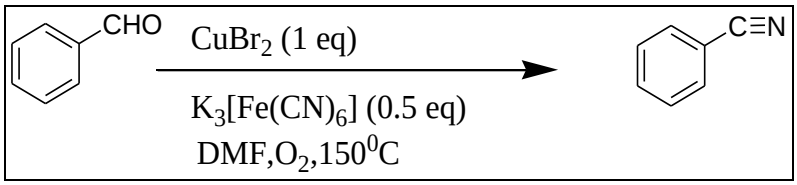
Scheme. II. A. 19. Schmidt type synthesis conversion of aldehyde to nitrile

There are also other methods present (e.g. J. Kim et al reported condensation of an aldehyde with NH_4OAc using catalytic amount of $NaNO_2$, HNO_3 and 4-AcNH-TEMPO under dioxygen atmosphere produces nitrilesselectively; scheme. II. A. 20) [21].



Scheme. II. A. 20. Condensation of aldehyde with NH_4OAc to get nitriles

J. You et al. describe the direct conversion of aldehyde with a copper promoted -CN bond cleave of cyanide ion from coordination complex in dioxygen atmosphere (scheme. II. A. 21) [22].



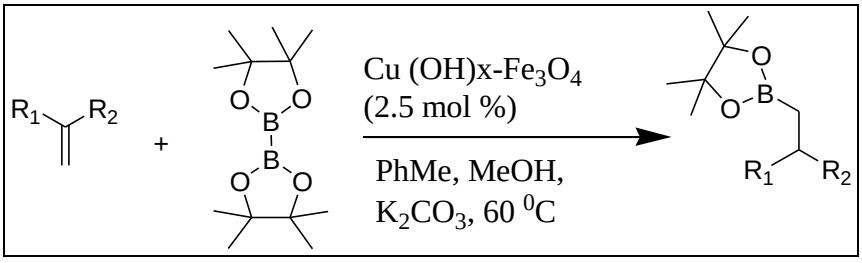
Scheme. II. A. 21. Copper promoted nitrile formation from aldehyde.

II. A. 6. Reaction catalysed by Fe_3O_4 nano-particle:

Magnetic nanoparticles (MNPs) of Fe_3O_4 are attractive growing interest in recent years in many different fields owing to their intrinsic properties such as low toxicity, high surface area and easily availability of starting material for their preparation. Besides, superparamagnetic behaviours of the nano particles are allow controlling their motion by an external magnetic field. In catalytic prospectus, this is translated into an easy recovery and separation from the reaction medium by magnetic decantation. Additionally, almost all ferrites behave as metal oxides with a large number of hydroxyl groups on their surfaces. This characteristic allow to build a well-defined shell of other materials around the ferrite core, also helps to grafting functional groups and make it suitable for the supporting of all kinds of ligands, catalysts and actuators, by covalent bonds. For this unique physical property of magnetite, they appear as an interesting, reusable and easily recoverable catalyst for many reactions. Recent literature survey reveals the catalytic usage of MNPs particles in many reactions, such as for addition, oxidation and also for coupling reactions.

II. A. 6. 1. Application of Fe_3O_4 nano-particle for addition reaction:

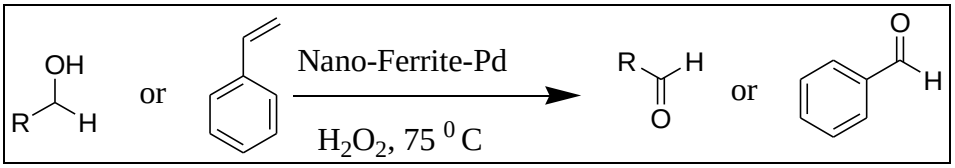
M. Yus et al. recently reported the catalytic effect of magnetite impregnated with copper towards the addition reaction of C=C and alkoxydiboron (scheme. II. A. 22) [23]. Again, M. Yus and co-workers use the same catalyst for propargyl-amines via a multicomponent reaction [24].



Scheme. II. A. 22. Cu impregnated-Fe_3O_4 catalysed addition reaction.

II. A. 6. 2. Application of Fe_3O_4 nano-particle for oxidation reaction:

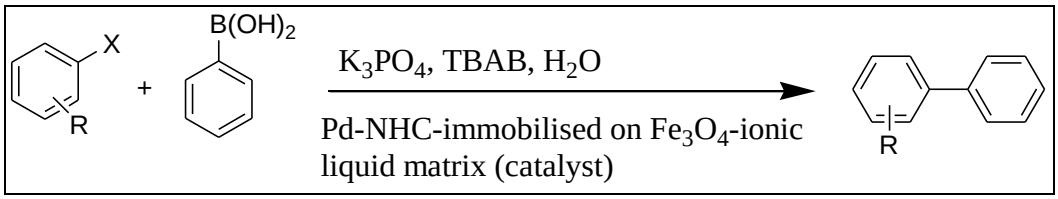
Magnetic nanoparticle supported-Pd catalysed oxidation of alcohol/olefin to their corresponding aldehydes has also been reported by R. S. Varma et al., (scheme. II. A. 23) [25].



Scheme. II. A. 23. Nano magnetite supported-Pd catalysed oxidation reaction.

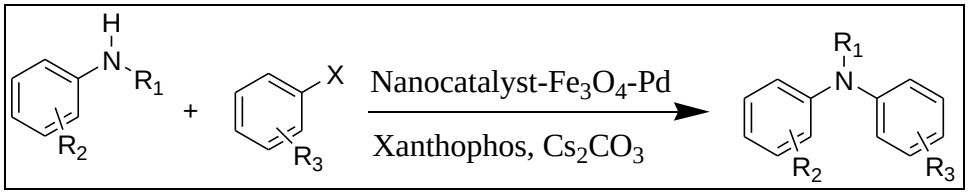
II. A. 6. 3. Application of Fe_3O_4 nano-particle for coupling reaction:

M. Beller and co-workers reported coupling of sulfonamides and alcohol using nano Ru/Fe_3O_4 catalyst [26]. M. J. Jin et al. reported the effectiveness of magnetite nanoparticle ionic liquid matrix immobilized Pd-NHC catalyst for Suzuki reaction in water (scheme. II. A. 24) [27].



Scheme. II. A. 24. Suzuki reaction in water medium

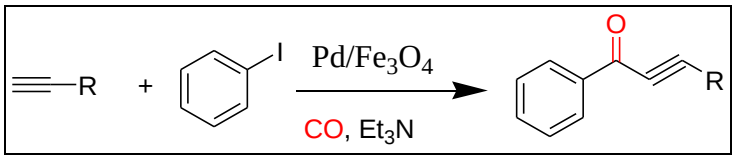
Again, Gawande et. al., used Pd-magnetite nano-catalyst for Buchwald-Hartwig type amination reaction of amines/ amides (scheme. II. A. 25) [28].



Scheme. II. A. 25. Magnetite immobilized Pd catalysed Buchwald-Hartwig amination reaction.

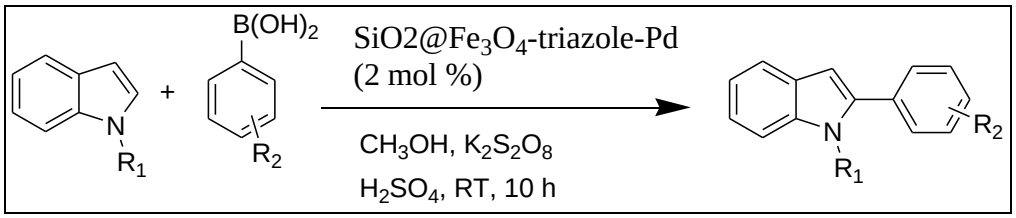
Moreover, there are so many literatures are present regarding the uses of magnetic nano-particle for Sonogashira (e.g., Liu and colleagues developed magnetically retrievable super magnetic Pd/Fe_3O_4 nano-catalyst and successively used in carbonylative Sonogashira coupling reaction as a catalyst; scheme. II. A. 26) [29], Stille (e.g., Pd-SiO_2/Fe_3O_4 catalysed cross-coupling of

arylchlorides (for both electron-deficient and electron-rich) with organo-stannanes)[30], Hiyama (e.g., Zhang et al., used Fe_3O_4@ SiO_2-$Pd(OAc)_2$ nano-catalyst for Hiyama coupling) [31], Ullmann (e.g., Gawande et al., synthesized Fe_3O_4-CuO nano-catalyst in aqueous medium using inexpensive material and checked its catalytic activity for Ullmann type condensation reaction)[32], C-O (e.g., Sharma et. al., reported the catalytic usages of Cu-2QC@Am-SiO_2@Fe_3O_4 nano-catalyst for the reaction of 2-carbonyl substituted *β*-keto-ester/phenol and formamides) [33] and C-S (e.g., Varma and Baig reported C-S coupling of substituted aryl halides and thiophenols catalysed by Fe_3O_4-DOPA-Cu nano-catalyst) [34] coupling reactions.



Scheme. II. A. 26. Carbonylative Sonogashira coupling reaction catalysed by Pd/Fe_3O_4 nano-catalyst.

In addition, with above mentioned reactions magnetite nano particle also proved its utility for other coupling reactions; such as, SiO_2@Fe_3O_4-triazole-Pd catalysed cross coupling reaction between substituted phenylboronic acid and N-substituted indole (scheme. II. A. 27) [35].



Scheme. II. A. 27.SiO_2@Fe_3O_4-triazole-Pd catalysed cross coupling reaction.

II. A. 7. Other application of Fe_3O_4 nano-particle:

Besides, synthetic uses magnetite nanoparticles also have medicinal uses, such as M. G. Bawendi et al. recently developed a compact Zwitter ion coated magnetite nano-particle and discuss its biological activity [36]. Again, D.G. Anderson et al., recently reported the effectiveness of lipidoid-coated magnetite nanoparticle for DNA and s-RNA delivery [37]. Furthermore, T. Hyeon and co workers describe the extremely high r_2 relaxivity of ferrimagnetic iron oxide nano-cubes for Highly Sensitive in Vivo MRI of Tumors [38]. S. O' Brien have developed and successfully

applied immune-targeted super magnetic iron oxide nano-particle for in-vivo MRI and potential drug delivery for kidney diseases [39]. Besides, carbon matrix implanted magnetic nanocrystal can acts as a super anode material for lithium-batteries [40]. The versatile catalytic activity, application in medicinal chemistry, magnetic recyclability and low toxicity make magnetite nano-particles as an ecological, industrial and economic benefit.

II. A. 8. Conclusion:

Nitriles are not only serving as biologically important functional group but also used as very useful intermediate for many functional group transformations and also for the preparation nitrogen containing heterocyclic compounds. From literature survey, it seems that most of the reported methodologies are suffered by one or more disadvantages such as use of strong oxidant, expensive catalyst and long reaction time and also by lack of straightforward process. Therefore, author felt the necessity to develop a milder protocol by using less toxic, inexpensive and environmentally benign Fe_3O_4-nano catalyst for the one-pot synthesis of nitriles.

Chapter II

Section B

(Fe_3O_4-nanoparticles catalyzed an efficient synthesis of nitriles from aldehydes)

II. B. Present investigation:

II. B. 1. Result and discussion:

Inendeavour of our work for our present investigation we chose an aldehyde as our primary precursor, hydroxylamine hydrochloride for nitrogen source and iron nanoparticles as catalyst. The nano particles were synthesized by reported methodology using CTAB as a stabilizer. The synthesized nanoparticles were then characterized by SEM (fig. II. B. 1.), TEM (fig. II. B. 2) and XRD (fig. II. B. 3.) analysis. SEM images reveal the particle size of Fe_3O_4 NP's are in between 20-35 nm. TEM images prove crystalline structure of nano particles. Also, comparisons of XRD images of our freshly prepared Fe_3O_4 nano with those from literature available data, confirms the purity of our prepared nano particles, i.e. absence of maghemite and hematite in our product. The quantification of Fe in Fe_3O_4-CTAB was evaluated byAtomic Absorption Spectroscopy (AAS) using Fe standard solution (fig. II. B. 4). The plot in (fig. II. B. 4) depict absorbance versus concentration of Fe in Fe_3O_4-CTAB Nps. From the absorbance data, the concentration of Fe in Fe_3O_4-CTAB has been found to be 3.7 ppm and the calculated percentage of Fe in Fe_3O_4-CTAB form the experimental data has found to be 74% by weight.

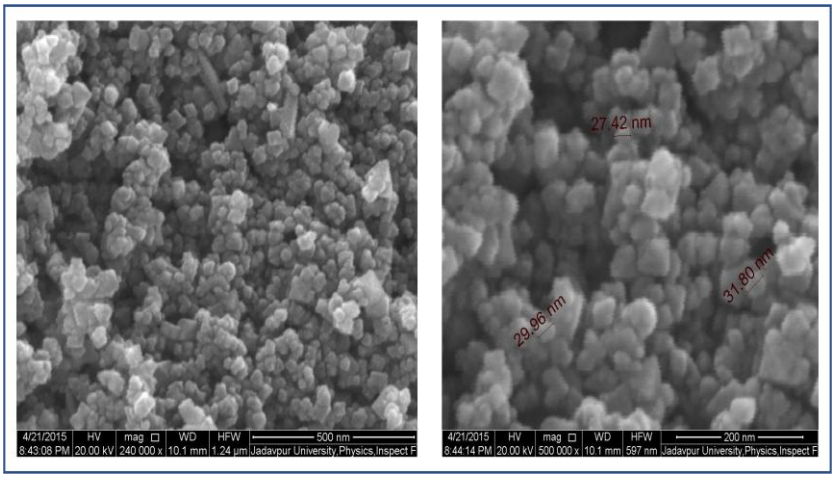


Fig. II. B. 1. SEM images of Fe_3O_4 nanoparticles.

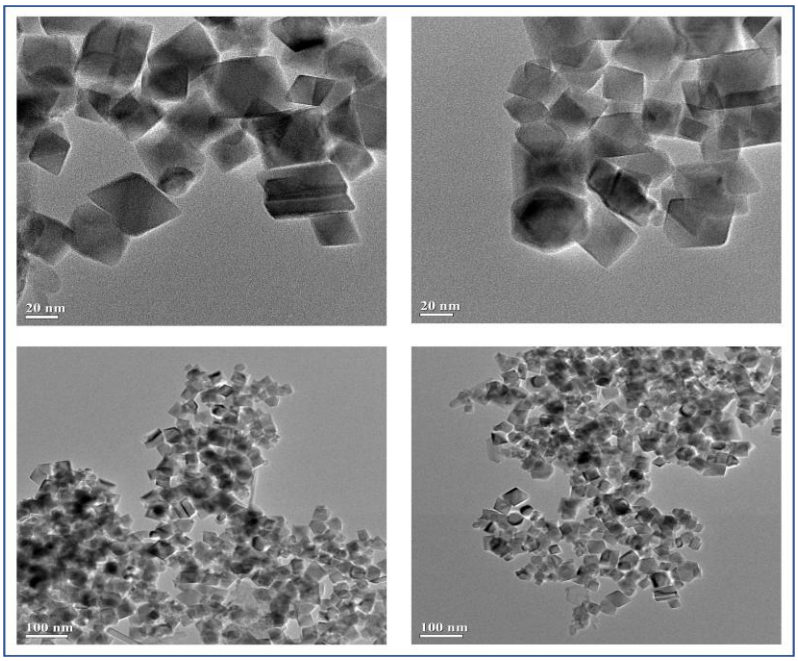


Fig. II. B. 2. TEM images of Fe_3O_4 nanoparticles.

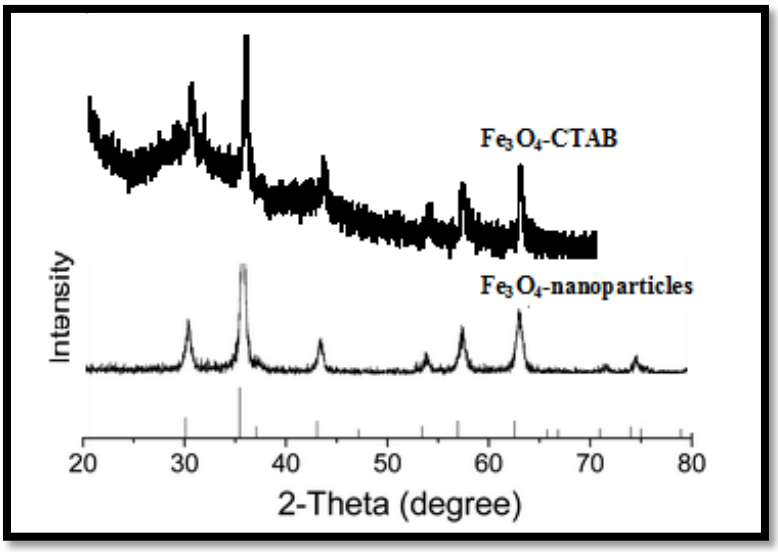


Fig. II. B. 3. XRD pattern comparison of literature XRD of Fe_3O_4 nanoparticles with synthesized Fe_3O_4-CTAB nanoparticles.

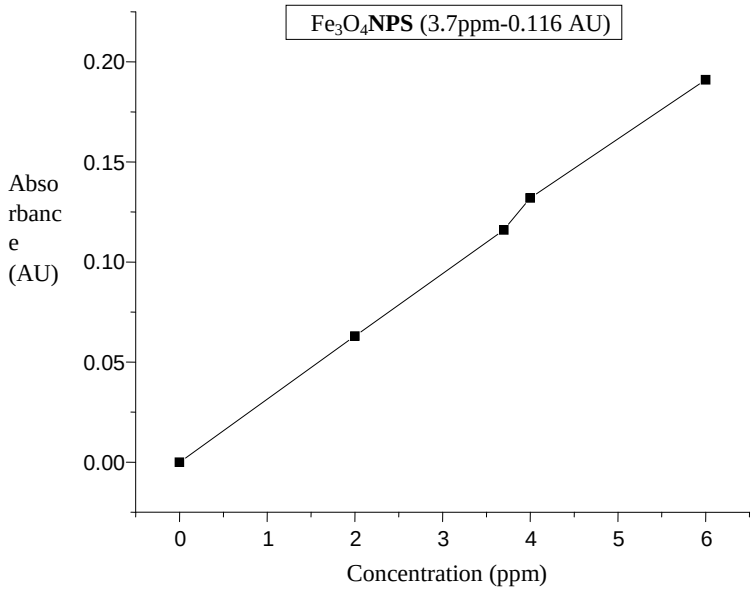


Fig. II. B. 4. AAS plot of Fe_3O_4 nano particle.

We had begun our present investigation with vanillin (0.5 mmol) as our model substrate, hydroxylamine hydrochloride (0.75 mmol) and Fe_3O_4 nanoparticles (7.4 mol %) in DMF (5 ml) and screened from room temperature to high temperature (table. II. B. 1). The excellent yield was found only at high temperature (entry 6, table. II. B. 1). At the low temperature range between 50-70 ^{o} C reactions furnish only oxime derivative and at 80-90 ^{o} C temperature range it offered a mixture of nitriles and oxime derivatives.

Table II. B. 1. Screening of catalytic activity of Fe_3O_4 nanoparticles [a]

Entry	Fe3O4-CTAB (mg)	$Fe3O_4$(mg)	Temp (^{o} C)	Time (h)	Yield (%)[b]
1	23.1	17.1	r.t	4	Nil
2	-	-	50	4	-
3	-	-	70	4	-

4	-	-	80	3	25
5	-	-	90	3	36
6	**-**	**-**	**reflux**	**2**	**97**

[a]reaction of vanillin (0.5 mmol), hydroxylamine hydrochloride (0.75 mmol) and Fe_3O_4-CTAB nanoparticles (23.1 mg) in dry DMF (5 ml) at different temperature. [b]isolated yield.

After reaching satisfactory result at reflux condition (table 1), catalytic potential of Fe_3O_4-CTAB nanoparticles was tested by reducing the amount of catalyst in similar reaction condition (table. II. B. 2). Finally, we were able to optimize the reaction condition and isolate 96 % yield of nitrile (entry 5, table. II. B. 2). Further reduction of the amount of catalyst or reaction time could not produce a better result (entry 6-9, table. II. B. 2). Finally, the combination of aldehyde (0.5 mmol), hydroxylamine hydrochloride (0.75 mmol) and Fe_3O_4-CTAB nanoparticles (1.8 mol %) and dry DMF (5 ml) under reflux condition offered the best result for our present investigation. For generalization of our scheme, we varied aldehydes **1a-o** and was successfully converted them to the corresponding nitriles **2a-o** under our optimized reaction condition (Scheme. II. B. 1 and table. II. B. 3).

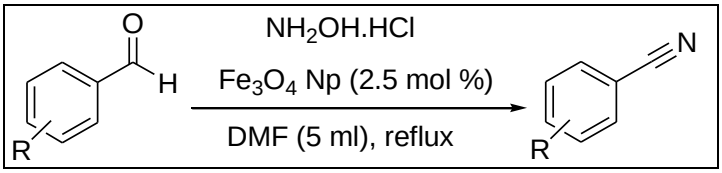
Table II. B. 2. Optimization of catalyst [a]:

Entry	Fe_3O_4-CTAB (mg)	Fe_3O_4(mg)	Time (h)	Yield (%)[b]
1	23.1	17.1	1.5	97
2	11.5	8.5	2	-
3	5.7	4.2	2	96

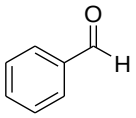
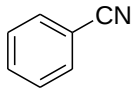
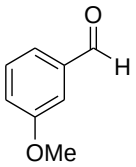
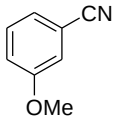
4	5.7	4.2	1.5	-
5	-	-	**1**	**96**[c]
6	-	-	0.5	91
7	3.4	2.1	2.5	88
8	2.3	1.5	4	83
9	1.1	0.8	4	78

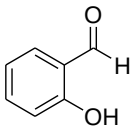
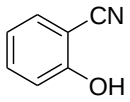
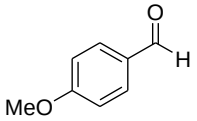
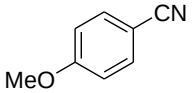
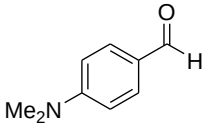
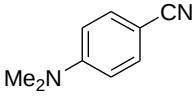
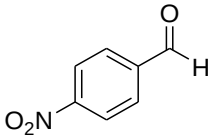
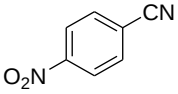
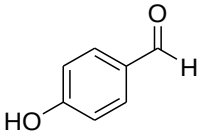
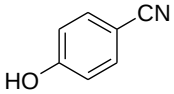
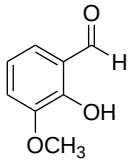
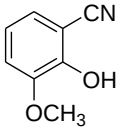
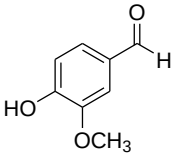
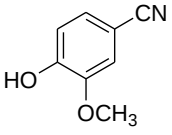
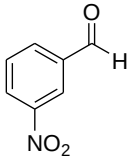
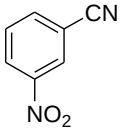
[a] Reaction of vanillin (0.5 mmol), hydroxylamine hydrochloride (0.75mmol) and Fe_3O_4 -CTAB nanoparticles in dry DMF (5 ml) under reflux condition. [b] Isolated yield. [c] Optimized reaction condition.

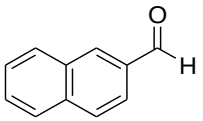
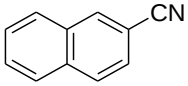
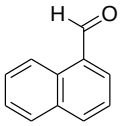
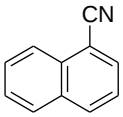
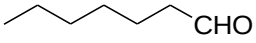
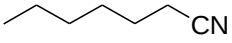
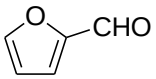
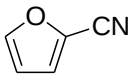
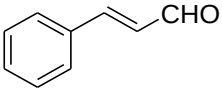
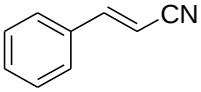
Table II. B. 3. Fe_3O_4 nanoparticles catalyzed synthesis of nitriles:



Scheme. II. B. 1. Fe_3O_4 Np catalyzed synthesis of nitriles from aldehydes.

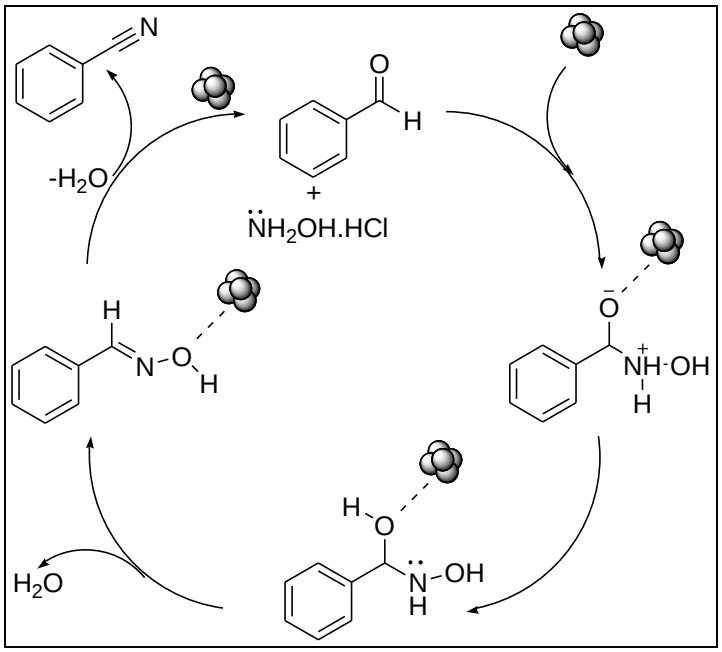
Entry	Aldehydes	Time (h)	Product	Yield (%) [b]
a		1		97
b		1		93

c		1.5		94
d		1.5		92
e		1.5		86
f		1		89
g		1.5		87
h		1		94
i		1		96
j		1.5		86

k		2		91
l		2		93
m		2		76
n		1.5		87
o		2		91

[b] Isolated yield

The plausible mechanism for the Fe_3O_4-CTAB nanoparticle catalyzed one-pot conversion of aldehydes into nitriles is shown in (**Scheme. II. B. 2)**. It includes the formation of N-substituted hydroxylamine in the intermediate step, which on dehydration gives aldoxime. On further dehydration of oximes furnished nitriles and back the catalyst.



Scheme. II. B. 2. Plausible mechanism for the synthesis of nitriles from aldehydes

II. B. 2. Experimental:

IR spectra were recorded on KBr disc in the range 4000-400 cm^{-1} on Shimadzu FT-IR 8300 Spectrometer. ^{1}H NMR and ^{13}C NMR were recorded on 500 and 300 MHz Bruker Advance FT-NMR Spectrometer using TMS as internal standard. SEM images were taken in FE-SEM INSPECT, F50, FEI. TEM images were taken inTEMJEOL JEM 2100 (200 kV). XRD was measured in XRD, Advance, D8, Bruker Germany. Atomic Absorption Spectroscopy was carried out in AAS50B, Varian.

II. B. 2. 1. Reaction procedure:

II. B. 2. 1. 1. General procedure for the synthesis of nitriles from aldehydes:

Aldehyde (0.5 mmol) and hydroxylamine hydrochloride (0.75 mmol) were added successively to a solution of Fe_3O_4-CTAB NPs (5.7 mg) i.e. Fe_3O_4 (1.8 mol %) in 5 ml dry DMF. The mixture was refluxed for appropriate time (table. II. B. 3). The progress of the reaction was monitored by TLC. After completion of the reaction, the solution was poured into 100 mL water and extract with ethyl acetate, washed several times with water. The combined organic mixture was dried over anhydrous Na_2SO_4, concentrated and the residue was purified by column chromatography

on silica gel 60-120 mesh using petroleum ether/ethyl acetate (95:5) as eluent to afford the pure nitrile. All the products were characterized by IR, ^{1}H NMR and ^{13}C NMR.

II. B. 2. 1. 2. Procedure for the preparation of Fe_3O_4-CTAB nanoparticles:

Solutions of iron (II) sulphate heptahydrate ($FeSO_4.7H_2O$, 1.67 g, 6×10^{-3} mol) in 50 ml deionized water, potassium nitrate (KNO_3, 1.01 g, 1×10^{-2} mol) in 10 ml of deionized water, and 2.5 M potassium hydroxide (KOH) were prepared. 1% (w/w) CTAB was mixed with the iron salt solution under vigorous stirring for two hours. To this solution, potassium nitrate was added and stirring was continued for another half an hour. Then, 10 mL of 2.5 M potassium hydroxide (2.5×10^{-2} mol) was slowly added to the above solution. The reaction mixture was heated to 100°C under nitrogen and maintained at this temperature for two hours. The nitrogen flow was then turned off and the mixture was cooled down to room temperature. After cooling, the black precipitate was repeatedly washed with deionized water, centrifuged and allowed to dry under vacuum at 50°C overnight.

II. B. 2. 1. 3. General Procedure for AAs:

Thesolution of Fe_3O_4-CTAB NPs in water was prepared by taking5 mg of the sample in 100 ml water and concentration of Fe used during the calibration was 0, 2, 4, 6 ppm.

II. B. 2. 2. Chemicals used for present investigation:

All the chemicals used in this investigation including their purity and sources are summarised in the following table (table. II. B. 4).

Table II. B. 4. Chemicals used in the present investigation:

Entry	Chemical	Sources	Purity (%)
1	Benzaldehyde	SRL	99
2	3-Methoxybenzaldehyde	Chemical Book	97
3	2-Hydroxybenzaldehyde	S.D. Fine	99
4	4-Methoxybenzaldehyde	Sigma-Aldrich	98
5	4- (N, N-Dimethyl amino) benzaldehyde	Sigma-Aldrich	99

6	4- Nitro benzaldehyde	LOBA chemie	98
7	4-Hydroxy benzaldehyde	S.D. Fine	98
8	2-Hydroxy-3-methoxy benzaldehyde	ACROS	99
9	4-Hydroxy-3-methoxy benzaldehyde	S.D. Fine	99
10	3-Nitro benzaldehyde	LOBA chemie	98
11	2-Npthaldehyde	Sigma-Aldrich	98
12	1-Napthaldehyde	Sigma-Aldrich	95
13	Cinnamaldehyde	S.D. Fine	99
14	Furfural	Sigma-Aldrich	99
15	Heptanal	Spectrochem	97
16	Fe-standard solution	Sigma-Aldrich	-
17	DMF	Merck	98
18	$CDCl_3$ for NMR	ACROS	99.8
19	Petroleum ether	Thomas Baker	98
20	Ethyl acetate	Thomas Baker	99
21	Silica-gel 60-120 mesh for column	SRL	-
22	Silica-gel for TLC	SRL	-

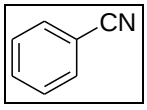
23	Na_2SO_4 anhydrous	SRL	99.5
24	KBr for FT IR	Merck	99
25	$FeSO_4$, $7H_2O$	SRL	98
26	KNO_3	Thomas Baker	97
27	KOH	Thomas Baker	98
28	CTAB	Sigma-Aldrich	99

II. B. 3. Conclusion:

In conclusion, author has developed an efficient protocol for one-pot conversion of aldehydes into nitriles using aldehydes (0.5 mmol), hydroxylamine hydrochloride (0.75 mmol) and Fe_3O_4-CTAB nanoparticles (1.8 mol %) using dry DMF (5ml) under reflux condition. Use of inexpensive and relatively less toxic nano-catalyst, easy reaction setup, excellent yield and effortless work-up process are the advantages of this protocol.

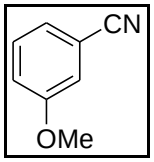
II. B. 4. Spectroscopic data of synthesized compounds:

II. B. 4. 1. Benzonitrile:



IR (cm^{-1},KBr): 3066, 2230(-CN), 1641, 1572. ^{1}H NMR (300 MHz, $CDCl_3$): δ, 7.34-7.47 (m, 2H), 7.56-7.62 (m, 3H) ppm. ^{13}C NMR (75 MHz,): δ, 112, 118, 128, 132, 133 ppm.

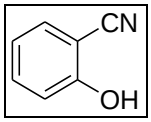
II. B. 4. 2. 3-Methoxy-benzonitrile:



IR (cm^{-1}, KBr): 2943, 2230 (-CN), 1596, 1578, 1290, 1265, 1044, 788, 682. ^{1}H NMR (300 MHz, $CDCl_3$): δ, 3.83 (s, 3H), 7.11-7.39 (m, 4H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ, 55.5, 113.4,

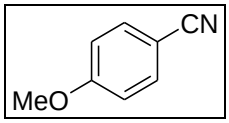
116.9, 118.7, 119.5, 124.2, 130.3 159.4 ppm.

II. B. 4. 3. 2-Hydroxy-benzonitrile:



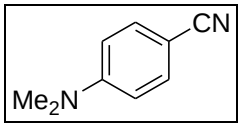
IR (cm^{-1},KBr): 3281 (-OH), 2231 (-CN), 1605, 1505, 1361, 1236, 848, 751, 668. ^{1}H NMR (300 MHz, $CDCl_3$): δ, 6.95-7.03 (m, 2H), 7.43-7.52 (m, 2H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ, 99.5, 116.4, 120.9, 132.9, 133.2, 134.7, 158.5ppm.

II. B. 4. 4. 4-Methoxy-benzonitrile:



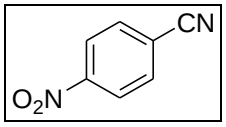
IR (cm^{-1},KBr): 2942, 2218 (-CN), 1606, 1509, 1305, 1258, 1177, 1024, 830, 683. ^{1}H NMR (500 MHz, $CDCl_3$): δ, 3.85 (s, 3H), 6.93-6.95 (d, 2H, J=9 Hz), 7.57-7.59 (d, 2H, J=9 Hz) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ, 55.5, 103.9, 114.7, 119.2, 133.9, 162.8 ppm.

II. B. 4. 5. 4-Dimethylamino-benzonitrile:



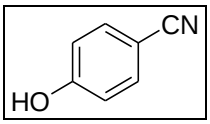
IR (cm^{-1},KBr): 2909, 2211 (-CN), 1608, 1527, 1371, 1173, 818. ^{1}H NMR (500 MHz, $CDCl_3$): δ, 3.04 (s, 6H), 6.67-6.7 (d, 2H, J=15 Hz), 7.46-7.49 (d, 2H, J=15 Hz) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ, 39.9, 97.4, 111.4, 120.6, 133.4, 152.5 ppm.

II. B. 4. 6. 4-Nitro-benzonitrile:



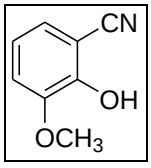
IR (cm^{-1},KBr): 3107, 2233 (-CN), 1602, 1526, 1349, 1295, 1106, 860, 682. ^{1}H NMR (500 MHz, $CDCl_3$): δ, 7.86-7.9 (d, 2H, J=15 Hz), 8.33-8.38 (d, 2H, J=15 Hz) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ, 116.7, 118.3, 124.3, 133.4, 150 ppm.

II. B. 4. 7. 4-Hydroxy-benzonitrile:



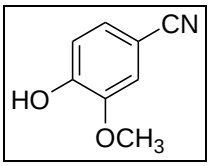
IR (cm^{-1},KBr): 3292 (-OH), 2234 (-CN), 1613, 1586, 1509, 1285, 1167, 838,702. ^{1}H NMR (500 MHz, $CDCl_3$): δ, 6.14 (s, 1H), 6.89-6.93 (d, 2H, J=15 Hz), 7.52-7.57 (d, 2H, J=15.5 Hz) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ, 103.4, 116.4, 119.2, 134.2, 159.9 ppm.

II. B. 4. 8. 2-Hydroxy-3-methoxy-benzonitrile:



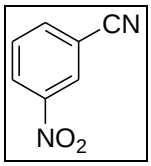
IR (cm^{-1},neat): 3351 (-OH), 2231 (-CN), 1611, 1591, 1492, 1070, 730. ^{1}H NMR (500 MHz, $CDCl_3$): δ, 3.92 (s, 3H), 6.32 (s, 1H), 6.87-6.9 (m, 1H), 7.02-7.04 (m, 1H), 7.08-7.1 (d, 1H, J=7 Hz) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ, 56.3, 98.6, 114.6, 115.9, 120.4, 123.9, 146.7, 148.9 ppm.

II. B. 4. 9. 4-Hydroxy-3-methoxy-benzonitrile:



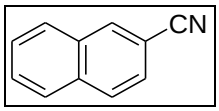
IR (cm^{-1},KBr): 3388 (-OH), 2227 (-CN), 1605, 1591, 1517, 1028, 819, 616. ^{1}H NMR (500 MHz, $CDCl_3$): δ, 3.93 (s, 3H), 6.1 (s, 1H), 6.95-6.97 (d, 1H, J=10 Hz), 7.08 (s, 1H), 7.22-7.26 (m, 1H) ppm. ^{13}C NMR (75 MHz,): δ, 56.4, 103.3, 113.7, 115.2, 119.2, 127, 146.6, 149.9ppm.

II. B. 4. 10. 3-Nitro-benzonitrile:



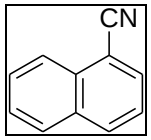
IR (cm^{-1},KBr): 3080, 2238 (-CN), 1618, 1534, 1356, 1102, 735. ^{1}H NMR (500 MHz, $CDCl_3$): δ, 7.71-7.76 (m, 1H), 7.98-8.01 (m, 1H), 8.46-8.5 (m, 1H), 8.53-8.84 (m, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ, 114.2, 116.5, 127.1, 127.3, 127.6, 130.6, 137.6 ppm.

II. B. 4. 11. Napthalene-2-carbonitrile:



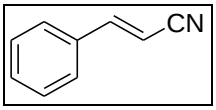
IR (cm^{-1},KBr): 2226 (-CN), 1594, 1500, 1273, 966, 826, 755, 643. ^{1}H NMR (500 MHz, $CDCl_3$): δ, 7.58-7.67 (m, 3H), 7.88-7.93 (m, 3H), 8.23 (s, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ, 109.3, 119.2, 126.3, 127.6, 128, 128.4, 129, 129.1, 132.2, 134.1, 134.6 ppm.

II. B. 4. 12. Napthalene-1-carbonitrile:



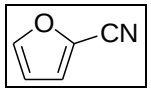
IR (cm^{-1},neat): 3061, 2222 (-CN), 1590, 1512, 1375, 1213, 801, 771. ^{1}H NMR (300 MHz, $CDCl_3$): δ, 7.48-7.7 (m, 3H), 7.88-7.92 (m, 2H), 8.06 (d, 1H, J=8.1 Hz), 8.22 (d, 1H, J=8.4 Hz) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ, 110.1, 117.8, 124.9, 125.1, 127.5, 128.5, 128.6, 132.3, 132.6, 132.9, 133.2 ppm.

II. B. 4. 13. Cinnamonitrile:



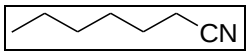
IR (cm^{-1},neat): 2925, 2216 (-CN), 1448, 1622. ^{1}H NMR (300 MHz, $CDCl_3$): δ, 5.85-5.95 (d, 1H, J=16.7 Hz), 7.26-7.68 (m, 6H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ, 96.3, 118.1, 127.7, 128.8, 131.2, 133.4, 150.6 ppm.

II. B. 4. 14. Furan 2-carbonitrile:



IR (cm^{-1}, neat): 2930, 2241 (-CN), 1653, 1095. ^{1}H NMR (300 MHz, $CDCl_3$): δ, 6.58 (s, 1H), 6.84 (s, 1H), 7.64 (s, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ, 112.7, 118, 119.6, 136.8, 146ppm.

II. B. 4. 15. Heptanenitrile:



IR (cm^{-1}, neat): 2926, 2246 (-CN), 1453, 1182. ^{1}H NMR (300 MHz, $CDCl_3$): δ, 0.89-2.47 (m, 13H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ, 14, 14.2, 22.6, 23.4, 25.8, 32.2, 119.5 ppm.

II. B. 5. Supporting Spectra:

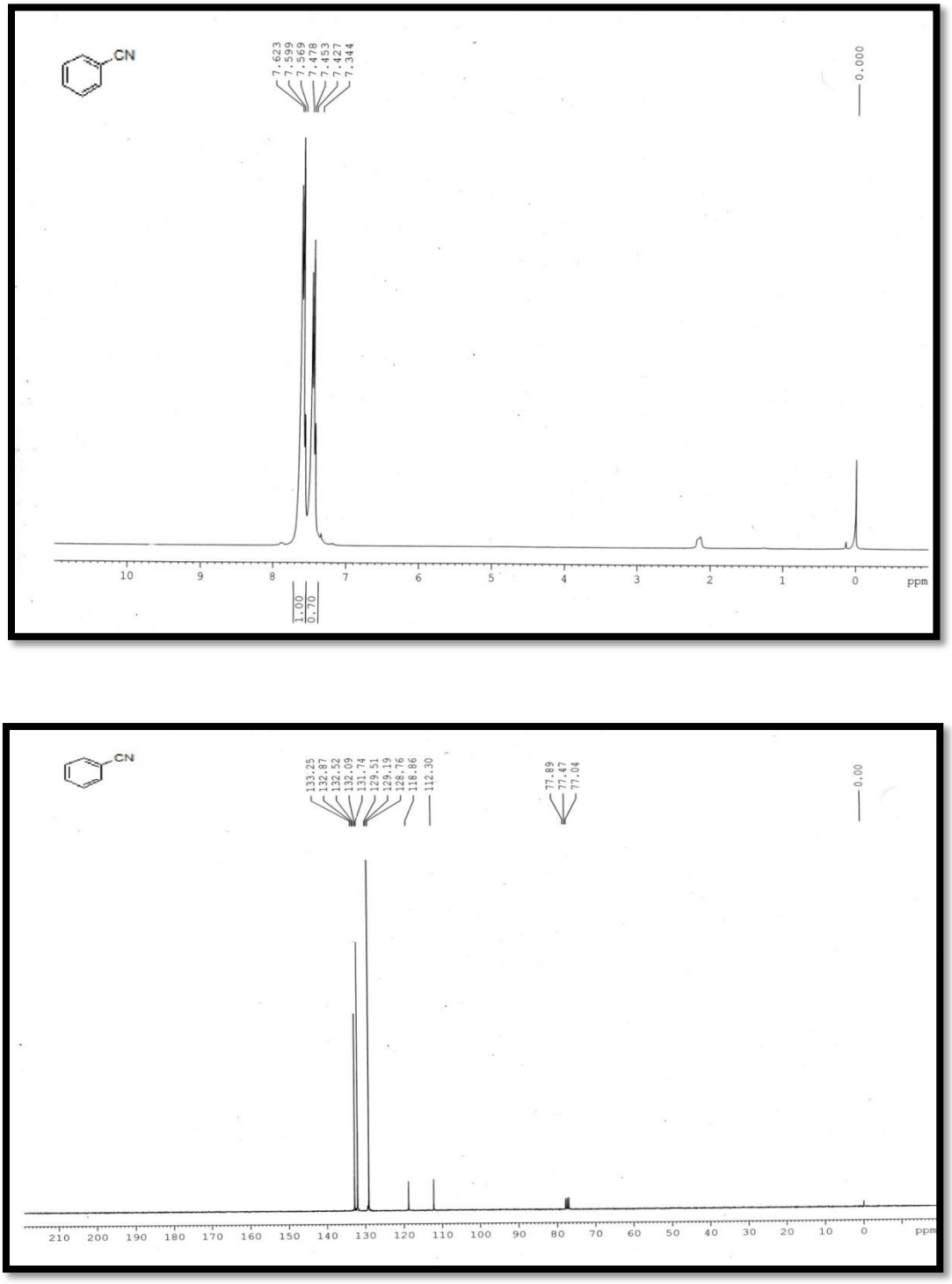


Fig. II. B. 5. ^{1}H and ^{13}C NMR spectra of Benzonitrile

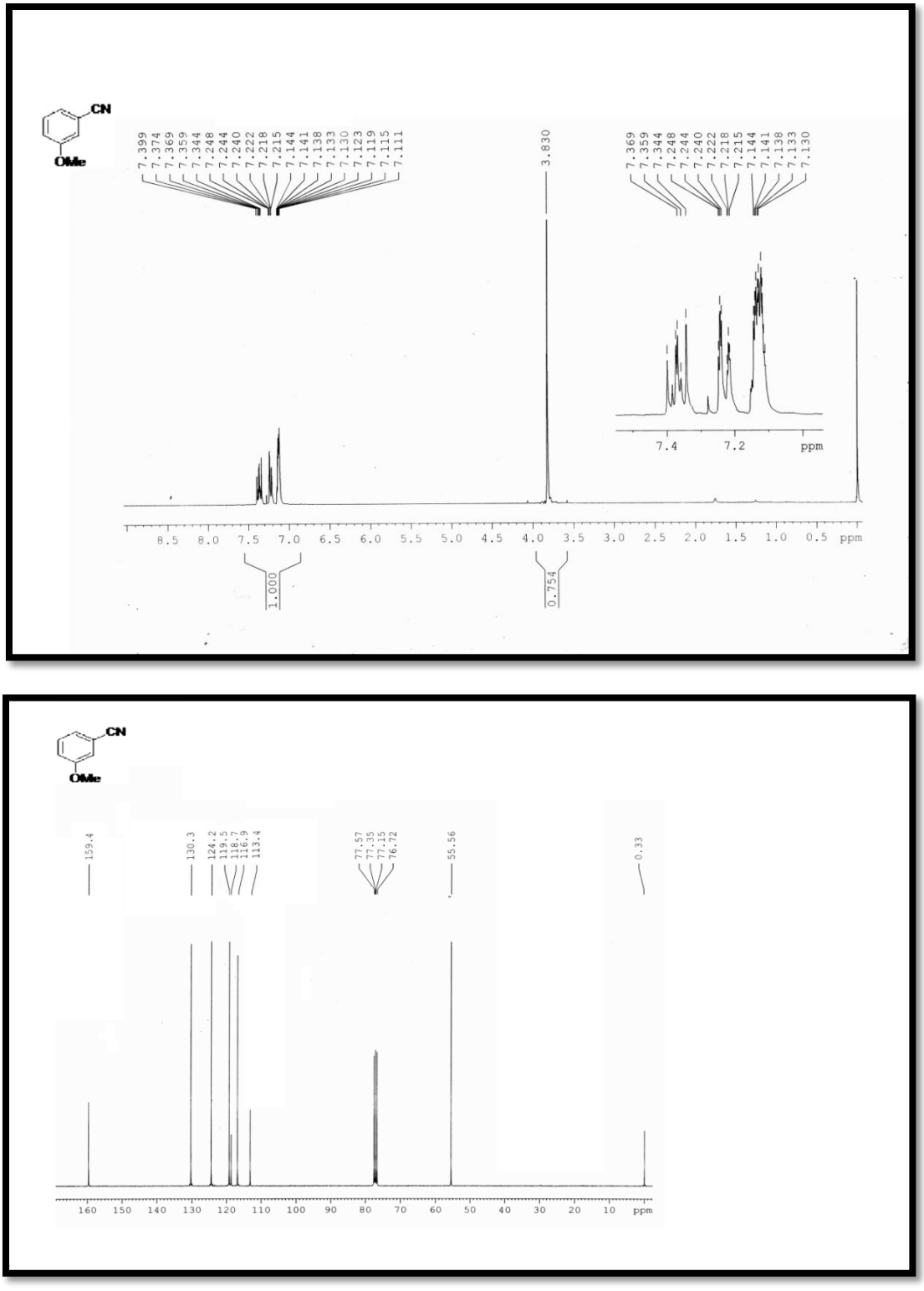


Fig. II. B. 6. ^{1}H and ^{13}C NMR of 3-methoxy benzonitrile

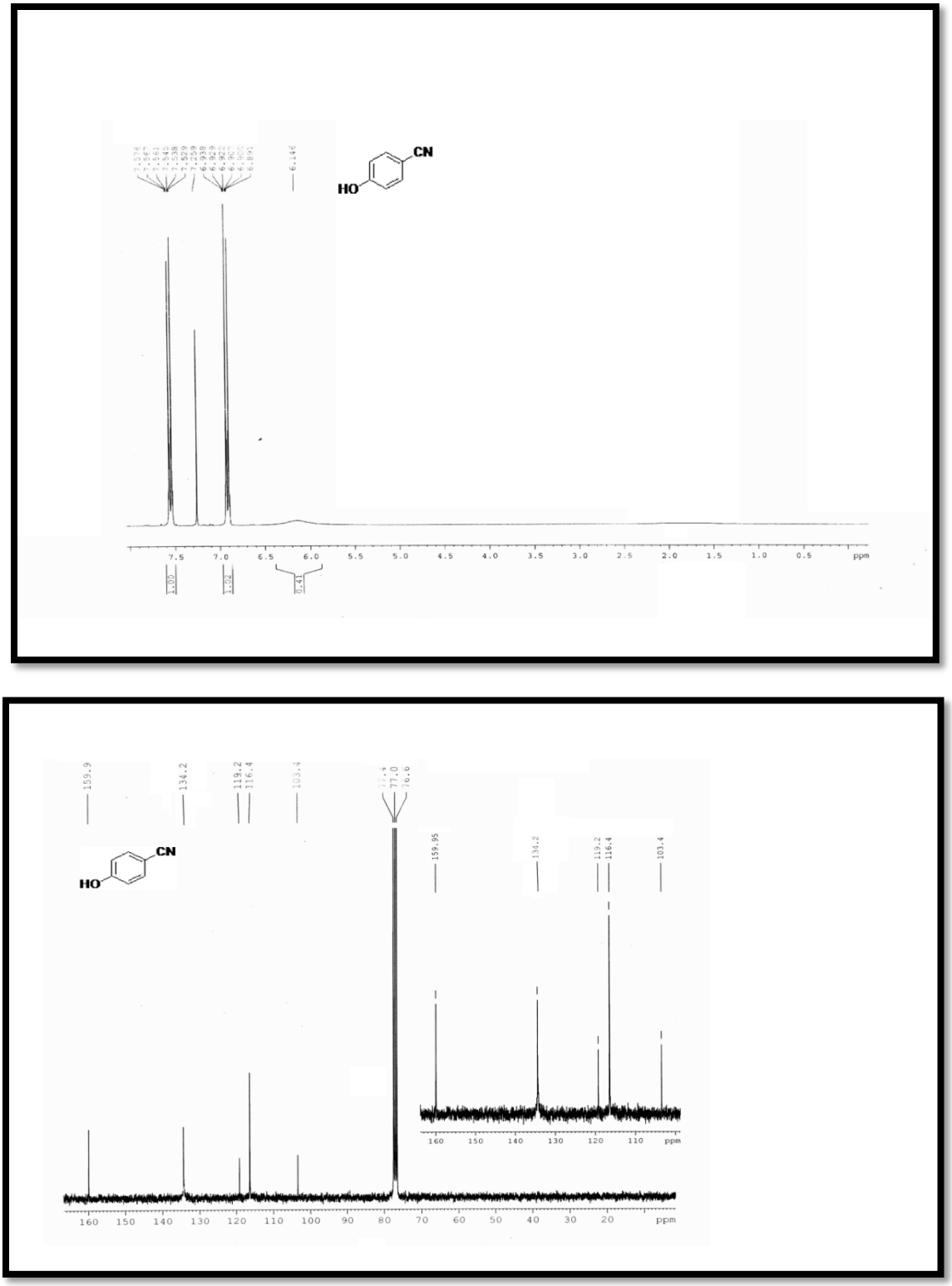


Fig. II. B. 7. ^{1}H and ^{13}C NMR of 4-hydroxy benzonitrile

Chapter III

3, 5 Di-nitrobenzoic Acid Derived Copper II Complex Catalyzed One pot multi components Synthesis of 2, 4, 5-trisubstituted Imidazoles Under solvent-free conditions

Section A

(General introduction and synthetic background of imidazole)

III. A. 1. A general introduction of imidazole:

III. A. 1. 1. Imidazole:

Imidazole is colourless and water soluble organic diazole compound with molecular formula $C_3H_4N_2$. It is an aromatic heterocyclic compound and belongs to the alkaloid family. The imidazole substructure serves an important building block for many biological important moieties such as histidine.

III. A. 1. 2. Structure:

Imidazole has a planar 5-membered ring structure in two equivalent tautomeric forms (due to the dislocation of N-H proton on either of the two N-atoms). It is a highly polar compound having dipole moment of 3.61D. Besides, the presence of a sextet of π-electrons, make imidazole an aromatic compound. The resonating structures of imidazole are as follows (Fig. III. A. **1**):

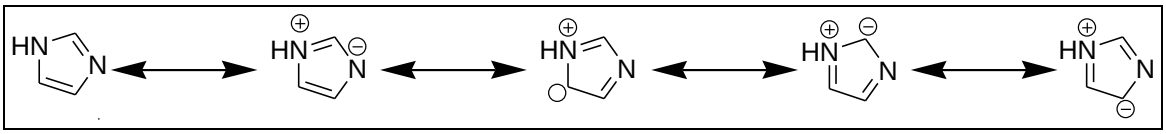
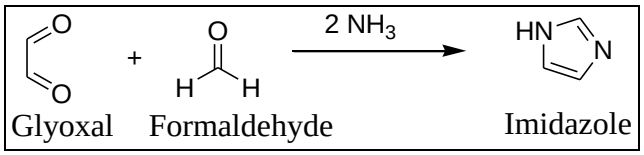


Fig. III. A. 1: Resonating structure of imidazole.

III. A. 2. Synthetic background of Imidazole:

III. A. 2. 1. Classical method for the preparation of imidazole:

Heinrich Debus, in 1858 [1] firstly synthesized imidazole by using a dicarbonyl compound, an aldehyde and ammonia. He used glyoxal as the dicarbonyl precursor and formaldehyde as the aldehyde (scheme. III. A. 1).



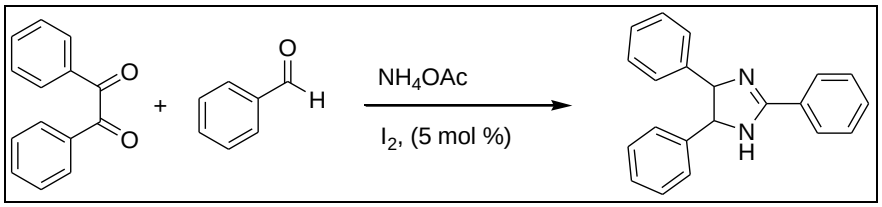
Scheme. III. A. 1. Debus process for imidazole synthesis

III. A. 2. 2. Modern methods for imidazole synthesis:

The diverse application in material, pharmacological and biological activities associated with the imidazole scaffold encourages the researcher to developa convenient and more useful synthetic route for imidazole and their derivatives. Since the first reported method by Heinrich Debus numerous techniques have been developed for the synthesis using diverse precursors and catalytic system.

III. A. 2. 3. Method for preparation of 2, 4, 5-trisubstituted imidazole:

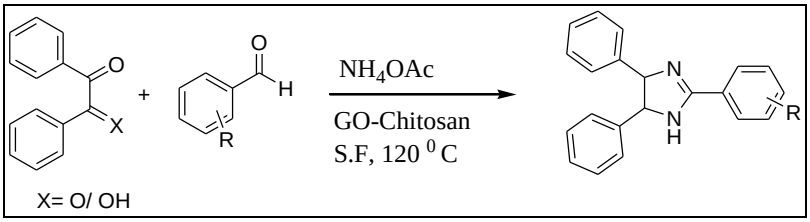
The combination of substituted 1, 2-diketones with other combining chemical partner is the best fit for the synthesisof 2, 4, 5- trisubstituted imidazole. Literature survey revealed numerous catalytic systems are applied for the protocol. Recently, A. M. Chermahani et al. [2] using Zeolite nano crystalline zirconia and clay as their catalyst for preparation of 2, 4, 5-trisubstituted imidazole. Again, Tej p. Singh et al. have reported the use of molecular iodine as an efficient catalyst for the preparation (scheme. III. A. 2). [3]



Scheme. III. A. 2. Molecular iodine catalysed preparation of 2, 4, 5- trisubstituted imidazole.

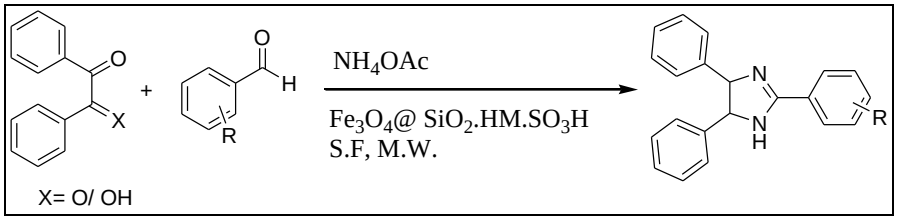
Besides, M. S. Singh et al. used L- Proline as a catalyst [4] for the one pot synthesis of 2, 4, 5-trisubstituted imidazole. Moreover, Mohammad Barekatet et al. [5] used sodium dihydrogen phosphate (NaH_2PO_4) as their potent catalyst for the preparation of imidazoles. Also, other metal catalysed reactions are available for the 2, 4, 5-trisubstituted imidazole synthesis (such as; InF_3 as reported by Yeon Tae Jeong et al. used in their methodological investigation [6]; $Zr(acac)_4$ is another useful catalyst used by Ahmad R. Khosropour et al. for the synthesis[7]; besides, Majid M.

Heravi et al. [8] used $NiCl_2$, $6H_2O$ and E. Rafiee et al. [9] used Fe_3O_4 as their potential catalyst for synthesis of tri-substituted imidazole). Besides this some solid supported catalyst are also used for the preparation. Just like, Ali Maleki et al. (scheme. III. A. 3) [10]synthesized trisubstituted imidazole by the reaction of 1,2-diketone/ α-hydroxy ketone, substituted aldehyde and NH_4OAc using graphene oxide-chitosan bio-nanocomposite as a potential catalyst under solvent free condition. The protocol was equally applicable for both electron donating/ withdrawing group substituted aldehydes.



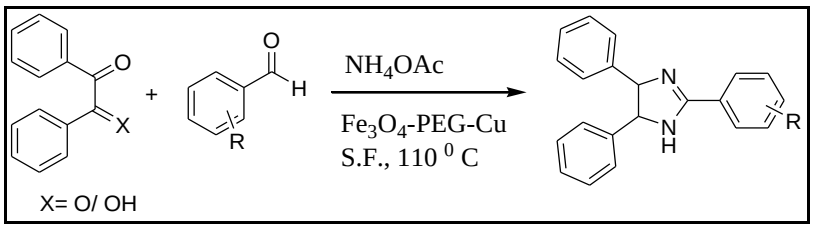
Scheme III. A. 3. GO-Chitosan catalysed preparation of trisubstituted imidazole.

Hossein Naeimi et al. (scheme III. A. 4) [11] used Fe_3O_4-SiO_2.HM.SO_3H as a heterogenous catalyst for preparation of trisubstituted imidazole under solvent free condition.



Scheme. III. A. 4. Synthesis of trisubstituted imidazole using Fe_3O_4-SiO_2.HM.SO_3H as a heterogenous catalyst

Moreover, Cu-nanoparticle supported on Fe_3O_4-polyethelene glycol nanocomposite as reported by J. Safari et al. severs well for substituted imidazole synthesis (scheme. III. A. 5) [12].



Scheme. III. A. 5. Synthesis of substituted imidazole using Fe_3O_4-PEG-Cu nano-composite

Beside this, there also other solid supported catalysts have reported for the 2, 4, 5-trisubstituted imidazole synthesis are e.g. Cu $(NO_3)_2$-zeolite [13], silica-H_2SO_4[14], mercaptopropyl silica [15]and SBA-15/TFE [16]etc.

Along with those catalytic processes there are some other techniques also available just as the microwave irradiation technique as reported by Scott E. Wolkenberg et al. [17] for the synthesis of tri- substituted imidazole.

III. A. 3. Uses of Copper salts as a catalyst:

The easy accessibility of Cu into various oxidation state (such as: Cu^{0}, Cu^{I}, Cu^{II} and Cu^{III}) allowing it to follow both radical pathways as well organometallic- intermediating bond-forming pathway similar that of palladium catalyst. Alongside with the change in oxidation state allowing copper to attached with different functional group through π- coordination or Lewis acids interaction. Thus, copper easily can conduct a number of different type chemical reactions.

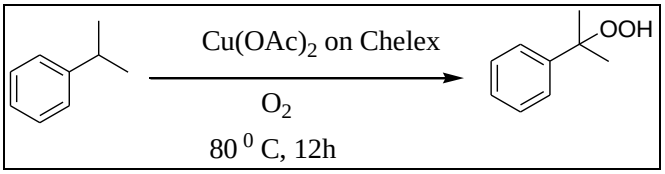
III. A. 3. 1. Copper catalysed oxidation reaction of benzylic, alkane, alkene, alkyne and arene C-H bond:

Suitable Copper catalysts are useful for oxidation of classes of hydrocarbons such as alkyl, alkynyl, benzylic, aryl andalkenyl.

III. A. 3. 1. 1. Benzylic C-H oxidation:

This type of reactions involves the oxidation of weaker C-H bond (e.g. X. Song et al. in their work reported the mild and highly efficient oxidation method for acidic benzylic compounds to their corresponding acids using Cu-phthalocyanine as a catalyst).[18] Besides there are other reported process are also available in which oxidation of a compound having benzylic hydrogen occurs using copper catalyst. Such as, Allara in 1972 reported the selective oxidation of fluorene to fluorenone.[19] Besides, Garcia et al. described the Cu(II)-1,3,5-benzenetricarboxylate a metal-organic framework catalysed oxidation of Xanthene, also they used the same catalyst for oxidation of fluorene.[20] Besides the oxidation of reactive benzylic substrates, there also examples of oxidation of non-reactive benzylic substrate are present (e.g. Cheng and co-workers reported oxidation of cumene to per oxo-cumene using $Cu(OAc)_2$ on chelex without using of any

radical initiator with maximum selectivity, scheme. III. A. 6).[21] Again, Zhang et al. describe the oxidation of toluene to corresponding acid through the use of $CuCl_2$ and a radical initiator HPPDO.[22] Moreover, recent literature reveals that by using suitable copper catalyst a benzylic substrate can also oxidized to their corresponding nitriles (e.g. Cu-impregnated zeolites catalysed conversation of toluene or its derivative to their nitriles as reported by Beschmann et al.).[23]



Scheme. III. A. 6. Oxidation of cumene using Cu (II)-catalyst

III. A. 3. 1. 2. Oxidation of alkane:

Higher C-H bond strength, lack of regioselectivity and formation of over oxidized product are the common issue for oxidation of alkane. Thus, several researches are developed to achiev a well-accepted protocol for this oxidation process using copper catalyst. Such as Sir Derek Barton and coworkers reported the use of Cu(II) chelates catalyst along with TBHP and O_2 for oxidation of saturated hydrocarbon.[24] Later, Komiya et al. reported the addition of crown ether to Cu (II) catalyst enhanced the selectivity of oxidation towards the required product.[25] Recently, Glatz et al. shown the use of modified Cu- SiCN ceramics can oxidized cyclo-alkanes to their corresponding ketones with a better yield.[26]

III. A. 3. 1. 3. Alkene oxidation:

III. A. 3. 1. 3. 1. Oxidation at allylic position:

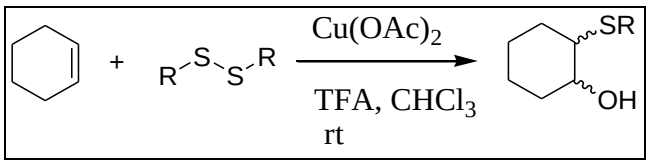
Presence of unsaturation, make the oxidation of allylic position of an alkene more difficult and need much milder condition than that for alkane or benzylic system. But using of copper catalyst for the process makes it more suitable in aspect of yield and selectivity. Such as Pozzi and co-workers reported the oxidation of allylic position of cyclohexene to corresponding ketone by the use of copper catalyst.[27]

III. A. 3. 1. 3. 2. Epoxidation of alkene:

As epoxides plays an important role in chemical industry, selectively epoxidation of alkenes thus gains an attraction in recent years. Copper catalytic epoxidation thus plays an important role in this regard. Just like Karandikar et al. reported the use of copper perchloro phthalocyanine complex on HSi-MCM-41 molecular sieves give promising result during the reaction. [28]

III. A. 3. 1. 3. 3. Oxidative di-functionalization of alkenes:

Oxidative di-functionalization is quite useful technique for insert heteroatom to hydrocarbons. There are several methods are present for the di functionalization (e.g. Bewic et al. reported the $Cu(OAc)_2$ catalysed hydroxy-sulfenylation of alkenes; scheme. III. A. 7) [29]



Scheme. III. A. 7. Hydroxy-sulfenylation of alkenes

III. A. 3. 1. 4. Alkyne oxidation:

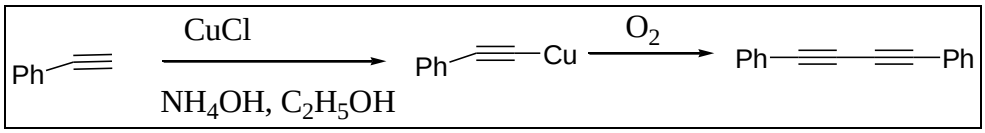
Aerobic oxidation of propargylic substances is quite complex in terms of overoxidation and alkyne reaction pathways. But literature survey reveals some useful methods using copper as a catalyst by which we can easily overcome those problems (e.g. oxidation of propargylic substrate to their corresponding ketones by using Cu(II) catalyst-in combination with NHPI as reported by Sakaguchi et al.). [30]

III. A. 3. 1. 5. Oxidation of arenes (Hydroxylation):

Hydroxylation of arenes is quite challenging due to stronger C-H bond and also in term of selectivity. Just like direct conversion of benzene to phenol gives hydroquinone, catechol etc. are also formed during the reaction as side product. Here copper catalyst provides a good alternative way for the reaction. For this reaction Cu (I) catalyst serves well (e.g. Sasaki and co-workers reported the direct conversion of benzene to phenol by using CuCl as a catalyst) [31] Besides, Orita et al. carry the same conversation using $CuSO_4$ and ascorbic acid. [32]

III. A. 3. 2. Copper Catalysed coupling reaction:

Another useful reaction for the functionalization of organic compound that is catalysed by copper is coupling reaction. Copper can catalyse both C-C and C-hetero (C-N, C-S or C-O) type coupling reaction. It was 1869 when Carl Glaser prepared Cu (I) salt of phenylacetylene which further exposure on air produced homo-coupled 1, 3-diyne product (scheme. III. A. 8) [33]



Scheme. III. A. 8. Homo-coupling reaction of copper product

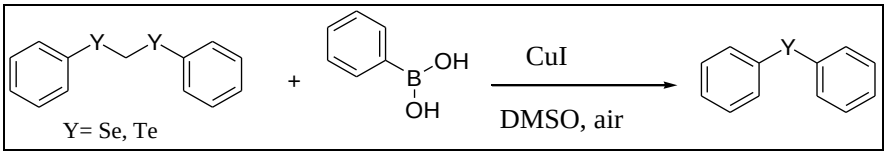
From then a number of modified methodologies are developed for this type of coupling reactions. Such as, Beifuss and co-workers have made a study of the effect of ligand and base on the above coupling reaction and find that TMEDA as the ligand of choice.[34] Besides, presence of other cocatalyst such as Ni (0)[35], iron [36] or palladium [37] enhance the rate of reaction during the homocoupling as well as for hetero-coupling of terminal alkynes. Again, in effort to find a greener alternative for the reaction methodologies Chen et. al., reported the solvent free technique for the coupling reaction[38]. Cadiot-Chodkiewiczhave reported the coupling of unsymmetrical di-ynes successfully [39]. Besides this cross-coupling reaction of alkynes with non-alkynyl substrate has also been reported (e.g. cross-coupling reaction of terminal alkynes with trifluoromethyl anion from CF_3-TMS)[40]. Recently, Stahl et. al., has reported the cross coupling of terminal alkynes with amides catalysed by $CuCl_2$ [41].

Along with this homo or hetero coupling of alkyne's there also other coupling reactions involving arenes and catalysed by Copper are available. Such as, cross-coupling reaction of arylboronic acid with arenes catalysed by Cu $(OCOCF_3)_2$[42] is reported. In addition, with this homocoupling of alkyl and vinylic substrate can also be catalysed by copper salts [43].

Another major utility of copper catalysed coupling reaction is the formation of C-N, C-O or C-S bonds using boronic acid derivatives/aryl halides, which offer new milder method with broad generality for C-hetero bond forming reactions. Such as, Collman and co-workers reported the N-arylation of imidazoles with arylboronic acid using copper (I) catalyst [44a], besides, Buchwald

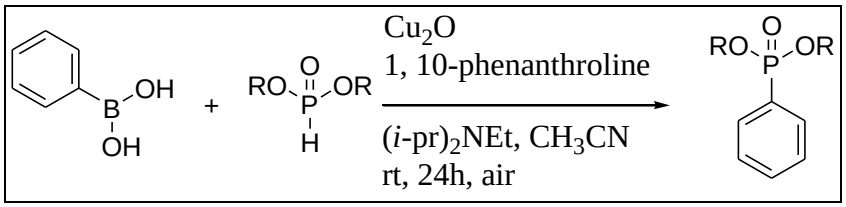
et. al. stated the N-arylation of indoles by the reaction of substituted indoles with aryl halide using CuI as the catalyst [44b] whereas that of for pyrazoles is reported by Taillefer et. Al.[44d] Again, CuCl in presence of DIPEA can enables easy aryl transfer to nitro enamines from hypervalent iodonium salts [44c]. With the realization of C-N bond formation, the next attempt was made for the oxidative coupling between -OH groups and arylboronic acid/aryl halides for C-O bond formation [45]**.** Like C-N or C-O bond forming reaction C-S bond forming reaction face the drawback related to poor yield due to the tendency of copper catalyst to oxidized thiol. This is overcome by the usage of oxidized sulphur species. Just like cross coupling of boronic acid derivative with sulfinate salt catalysed by $Cu(OAc)_2$[46a], whereas recently Feng et. al. successfully overcome the drawback regarding to oxidation of thiol and reported the S-arylation of thiols at room temperature using $CuSO_4$ as the potent catalyst [46b]. Sometimes using disulfides instead of thiol gives the better yield [47a, b]. Again, formation of diaryl thio-ethers can also possible by copper mediated reactions [47 c].

Another emerging uses of copper catalysed coupling reaction is the formation of organo selenium or tellurium product. Huang and coworkers described the cross coupling of boronic acid derivatives with aryl ditellurides and diselenides species to get respective organo compounds using CuI as a catalyst (scheme. III. A. 9) [48].



Scheme. III. A. 9. Copper catalysed formation of organo selenides and organo tellurides.

Other examples regarding to this C-hetero bond formation by using diverse boronic acid or selenium or tellurium species in presence of copper catalyst are available [49]. Further exploration of copper mediated coupling reactions led to the formation of C-P heteroatomic bond formation. Zhuang et. al., firstly reported the H-phosphonate diesters cross coupled with aryl boronic acid gives phosphonates (scheme. III. A. 10) [50].



Scheme. III. A. 10. C-P bond formation catalysed by copper

III. A. 3. 3. Other reactions catalysed by copper:

Suitable copper salt can also help to functionalized heterocyclic moiety through coupling reaction. Just as, demonstrating by coupling reaction of various amines [51]/ thiols [52] with azoles at 2-position catalysed by Cu (II) salt. In addition to this C-C coupling in azoles at 2-postion are also offered. Such as cross coupling of terminal alkynes with 1, 3, 4-oxadiazoles using Cu (II)-chloride under an oxygen atmosphere [53]. Along with this cross coupling, homocoupling of azoles can also carried out by application of copper catalyst [54].

III. A. 4. Conclusion:

Literature survey reveals that there are number of methodologies available for the synthesis of tri-substituted imidazole. But, harsh reaction conditions, tedious work up procedure, highly acidic medium, oxidizing environment, prolonged time period and uses of expensive reagents are the major disadvantages of the existing methods. Thus, to fulfill the insufficiency and to strengthen the synthetic methodologies and also influenced by the applicability of copper as a catalyst, author felt the necessity to develop a novel method for the synthesis of substituted imidazole using an polymeric Cu (II) complex prepared by us.

Chapter III

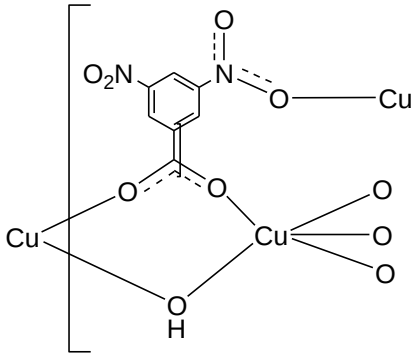
Section B

(Present work)

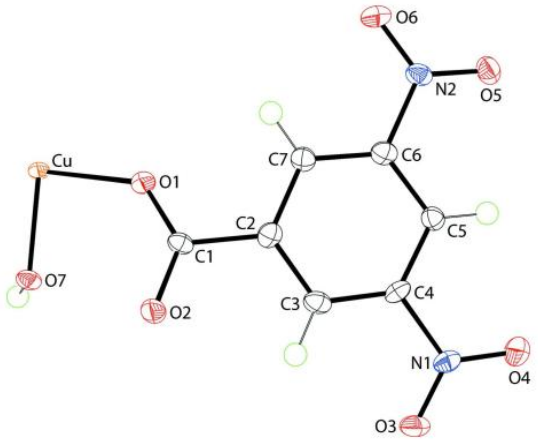
3, 5 Di-nitrobenzoic Acid Derived Copper II Complex Catalyzed One pot multi components Synthesis of 2, 4, 5-trisubstituted Imidazoles Under solvent-free conditions

III. B. 1. Result and Discussion:

In continuation of our effort to provide greener synthetic protocol for many reactions, we use indigenous Cu-complex as our catalyst for the present work (fig. III. B. 1a). The catalyst was prepared (see experimental section) and characterized by mass, XRD and SEM images. The crystallographic study shows that crystal asymmetric unit contains a Cu II cation, 3, 5-dinitrobenzoate and hydroxide anions shown by atom-labelling (fig. III. B. 1b). XRD data shows the core structural unit of each crystal has an orientation of Cu II ions in a Zigzag manner with hydroxide bridge along the c axis and chains of six-membered rings. Both of them are joined by the 'O' atom of the carboxylate group attached to the six-membered ring of the chain and Cu II ions of the Zigzag row (fig. III. B. 1c). Another Cu—O (nitro) bond connects the neighboring chains of the six-membered rings to each other (fig. III. B. 1c). Again, the presence of bifurcated O-H---O (nitro) hydrogen bonds gives an extra stability to the crystal structure (fig. III. B. 1d). Further characterization was done by Scanning Electron Microscope (Inspect F-50 FEI (Netherland) accelerating voltage of 10.00 kV and magnification of 20000X) image (fig. III. B. 2). SEM image of the Cu-complex show the stacking of the sheet like crystals. The width of the single crystal was measured in the range 120-125μm and the interfacial angle of the crystal was found to be 120.7^0 with hexagonal shape. The SEM image also confirms the crystalline morphology with regular surface of our Cu-catalyst.



Poly [(μ_3-3,5-dinitrobenzoatok^3 O^1:$O^{1'}$:O^3) (μ2-hydroxido-k^{2}O:O)-copper(II)]



(a) (b)

Fig. III. B. 1a: General structure of the prepared Cu-catalyst and (**1b**) Atom labelling image for asymmetric unit of the Cu-catalyst.

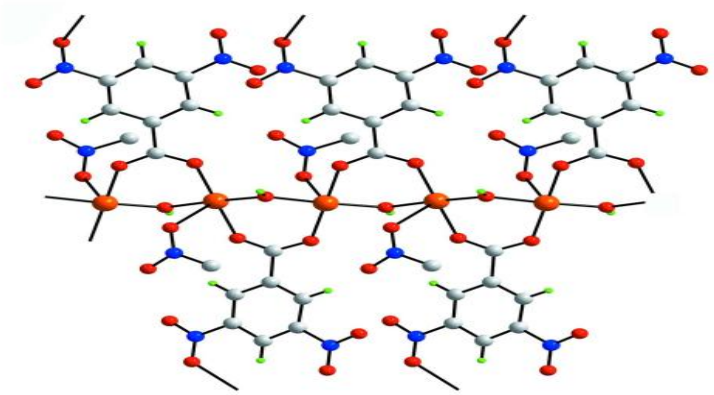


Fig. III. B. 1c: A Sight of zigzag chain along the c axis in the Cu II-complex with coordinating nitro group.

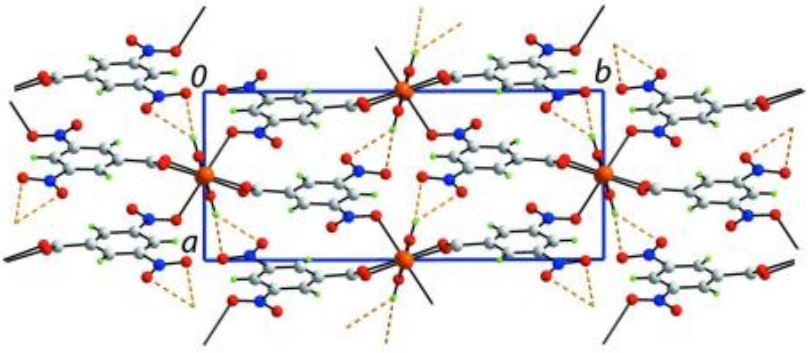


Fig. III. B. 1d: A View of the O—H···O(nitro) hydrogen bonds shown by the orange dashed lines present in the unit-cell of the Cu II-complex.

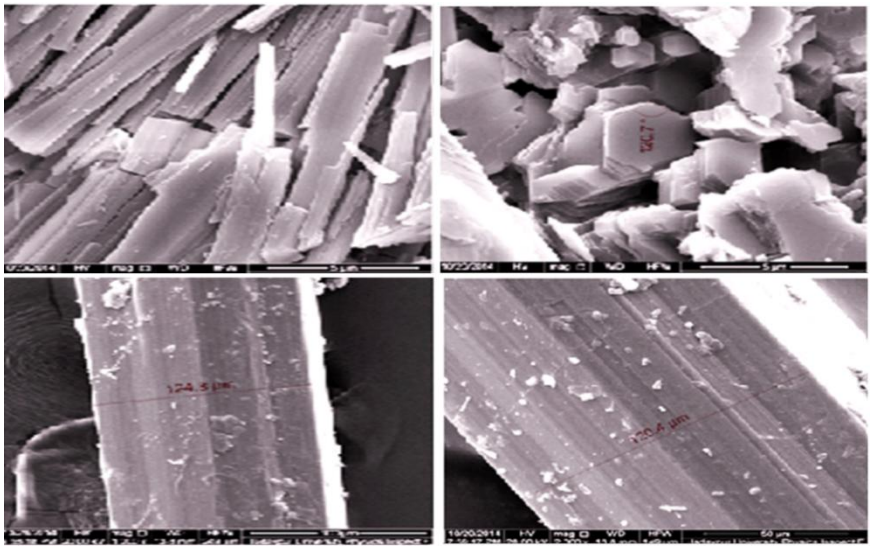
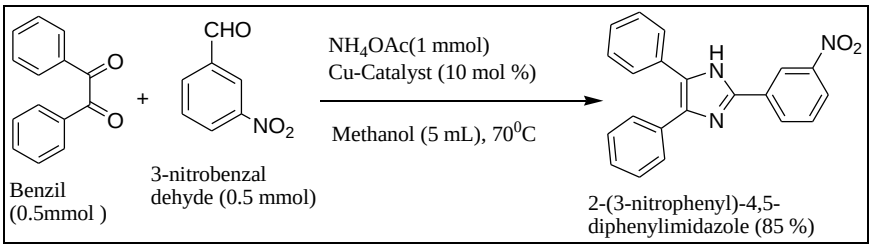


Fig. III. B. 2: SEM image of Cu-catalyst.

To assess feasibility, we initiate our reaction with benzil (0.5 mmol), 3-nitrobenzaldehyde (0.5 mmol) and NH_4OAc (1 mmol), in presence of our catalyst (10 mol %) using methanol (5 mL) as solvent at reflux condition and the desired product, i.e., 2, 4, 5-trisubtituted imidazole was isolated in 85% yield after 3 h. (scheme. III. B. 1). To reach the most effective reaction condition with our catalyst, we screening the same reaction (scheme. III. B. 1) using different medium (i.e., solvent/solid surface) with varying temperature (table. III. B. 1). Also, to find the most suitable nitrogen source for the reaction, we used different nitrogenous salts and found that NH_4OAc is more effective for the reaction. (table. III. B. 2).



Scheme. III. B. 1. Cu-catalyst catalysed synthesis of 2, 4, 5- trisubstituted imidazole from benzil

Table III. B. 1: Screening of reaction medium [a]:

Catalyst (mol %)	Medium	Temp(^{0}C)	Time(h)	Yield (%)[b]
10	Methanol	80	3	85
10	Acetonitrile	90	3$^{1/2}$	No reaction
10	Dichloro methane	80	3$^{1/2}$	45
10	Chloroform	80	3$^{1/2}$	Trace amount
10	**Silica-gel (for TLC) [c]**	**70**	**25min**	**97**

[a] Reaction of benzil (0.5 mmol), 3-nitrobenzaldehyde (0.5 mmol), NH_4OAc (1 mmol), our Cu-catalyst (10 mol %) and solvent (5 mL) [b] All yield is isolate yield[c] Silica-gel (for TLC) was taken: 1 gm.

Table III. B. 2: Evaluation of ammonium salts as a nitrogen source [a]:

Entry	Nitrogen source	Time (h)	Yield (%)[a]
1	NH_4Cl	$3^{1/2}$	Nil
3	$(NH_4)_2SO_4$	$3^{1/2}$	Nil
2	NH_4F	4	42
4	$(NH_4)_2CO_3$	_	38
5	NH_4HCO_3	_	35
6	NH_4HF_2	-	30
7	$(NH_4)_2HPO_4$	3	<20
8	NH_4SCN	_	35[c]
9	HCO_2NH_4	$4^{1/2}$	68
10	**NH_4OAc**	**25 min**	**97**

[a] Reaction of benzil (0.5 mmol), 3-nitrobenzaldehyde (0.5 mmol), our Cu-catalyst (10 mol %), Silica-gel (for TLC, 1gm) and ammonium salts (1 mmol) at 70^0 C.

[b] yields are isolated yield. [c] a mixture of product obtained

The catalyst shows the highest efficiency on silica-gel (for TLC) at 70^0c using NH_4OAc as a nitrogenous source. Influence, by the result on silica-gel surface, we ensue the effect of other solid surfaces on the Cu-catalyst for the reaction at same reaction condition. Now, we used Silica-gel (of various mesh sizes), alumina (acidic, basic, and neutral and HF), Zeolite-HY and montmorillonite (table. III. B. 3) as our solid surfaces. Result suggesting silica-gel (for TLC) as the most operative solid surface, for the catalyst during the three-component reaction.

Table III. B. 3: Effect of solid surfaces on Cu-catalyst [a]:

Entry	Catalyst + Solid-Surface	Time (min)	Yield (%)[b]
1[c]	**Silica-gel (for TLC)**	**25**	**97**
2[d]	Silica-gel (60-120)	60	45
3 [d]	Silica-gel (230-400)	75	60
4 [d]	Al_2O_3(neutral)	65	43
5 [d]	Al_2O_3 (acidic)	75	80
6 [d]	Al_2O_3(basic)	90	48
7 [d]	Al_2O_3 (HF)	65	80
8 [d]	Montmorillonite	75	46
9 [d]	Zeolite HY	60	82
10 [e]	SiO_2(for TLC)	120	35
11 [e]	SiO_2(60-120)	120	Nil
12 [e]	SiO_2(230-400)	120	10
13 [e]	Al_2O_3 neutral	120	12
14 [e]	Al_2O_3 acidic	120	15
15 [e]	Al_2O_3 basic	120	12

16 [e]	Al_2O_3-HF	120	30
17 [e]	Montmorillonite	120	38
18 [e]	Zeolite HY	120	28

[a] Reaction of benzil (0.5 mmol), 3-nitrobenzaldehyde (0.5 mmol), Cu-catalyst (10 mol %), NH_4OAc (1 mmol) and solid surfaces (1 g) at 70^0 C.

[b] isolated yield.

[c] got maximum yield.

[d] no further change observed, monitoring by TLC.

[e] Reaction without catalyst.

Further, the Scanning Electron Microscopic images (with Inspect F-50 FEI) of the catalyst over silica-gel after 1st run (fig. III. B. 3) has shown the aggregation of the catalyst on the silica surface. Moreover, the reusability of catalyst on silica-gel up to 5th runs as shown inthe graphical representation in (fig. III. B. 4), supports, the enhancement activity of catalyst on the silica-gel surface results by the immobilization of the catalyst through aggregation on silica-gel surface shown in (fig. III. B. 3).

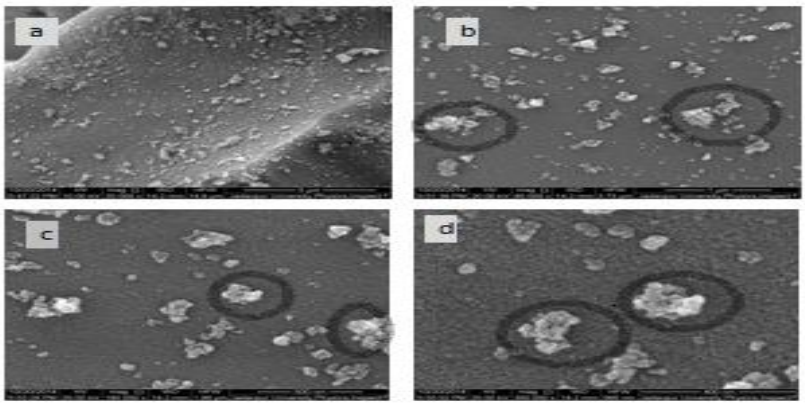


Fig. III. B. 3: SEM image of catalyst on silicagel after 1st run. Aggregation of catalyst are shown by the black circle

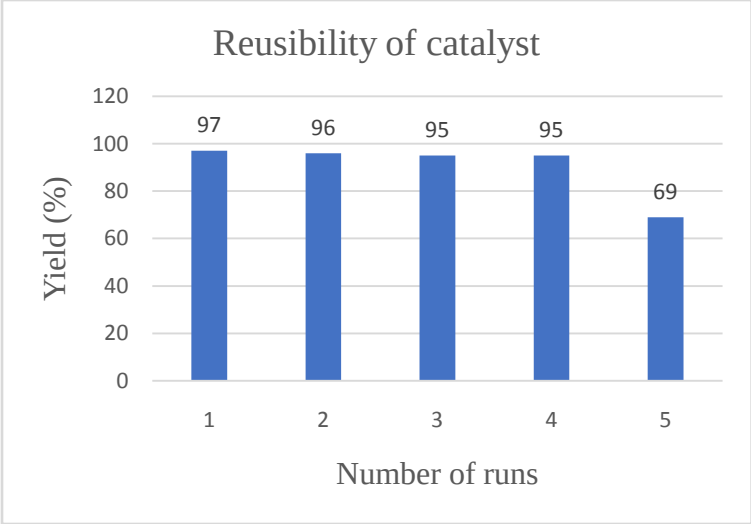


Fig. III. B. 4: Reusability of catalyst on silica-gel surface.

After reaching the satisfactory result at 70 ^{0} C over silica-gel (for TLC), the catalytic potential of catalyst was tested by decreasing both the amount of catalyst and silica-gel in similar reaction condition (table. III. B. 4). Finally, we get the optimized reaction condition and isolate 97 % yield of the desired product (Scheme 1). On further declined of the amount for any of the catalyst or silica-gel causes a drastically turn down of the yield. Thus, combination of benzil (0.5 mmol), aldehydes (0.5 mmol), NH_4OAC (1 mmol), Catalyst (2.5 mol %), silica-gel (for TLC, 750 mg) and 70 ^{0} C found to be the optimized reaction condition.

Table. III. B. 4: Optimization of the amount of catalyst and silica-gel [a]

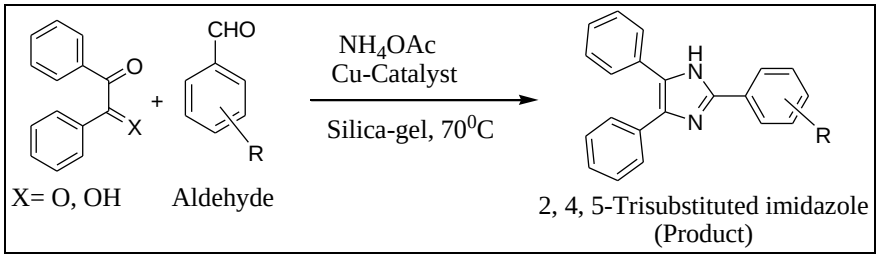
Entry	Silica-gel (g)	Catalyst (mol %)	Time (min)	Yield (%) [b]
1	1	10	25	97
2	_	5	25	97
3	_	2.5	45	94
4	_	2	45	75

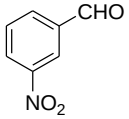
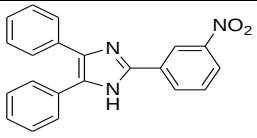
5	_	1	60	65
6	_	0.5	75	16
7	0.75	5	30	97
8 [c]	**0.75**	**2.5**	**20**	**97**
9	_	2	45	62
10	0.5	10	60	72

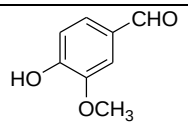
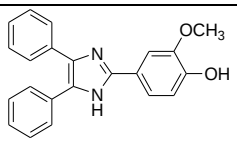
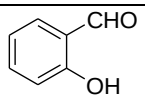
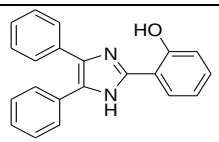
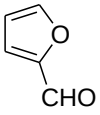
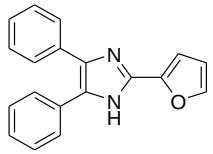
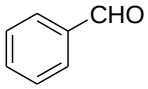
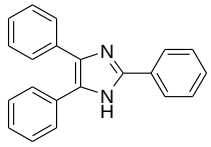
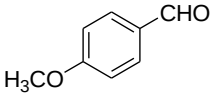
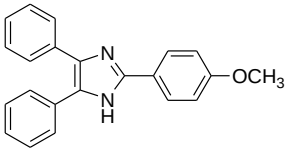
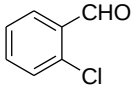
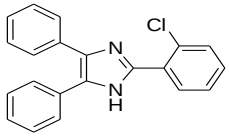
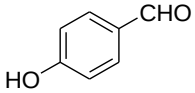
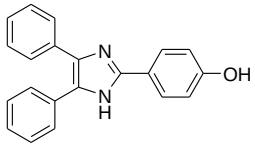
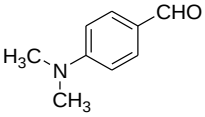
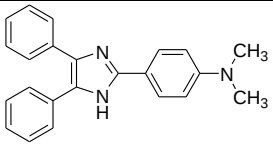
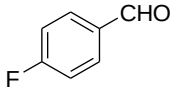
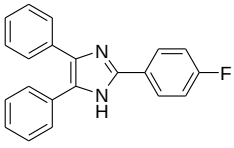
[a]reaction of benzil (0.5 mmol), 3-nitrobenzaldehyde (0.5 mmol), Cu-catalyst, Silica-gel (for TLC) and NH_4OAc (1 mmol) at 70^0 C, [b]isolated yield, [c] optimized reaction condition.

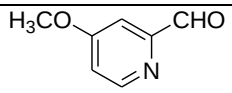
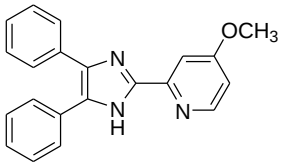
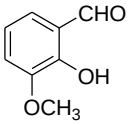
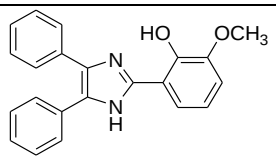
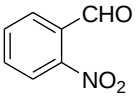
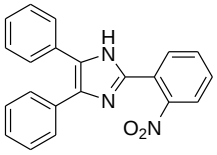
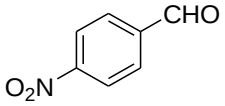
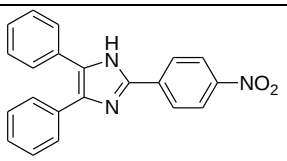
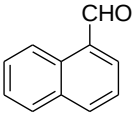
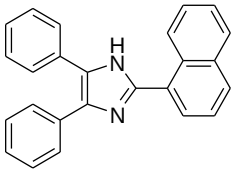
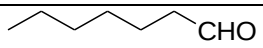
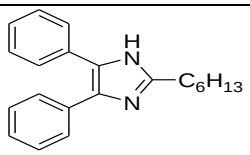
Further, Condensation reaction of benzil/benzoin with other aromatic aldehydes (bearing H, electron-withdrawing groups and electron-releasing groups); heterocyclic aldehydes using our optimized reaction condition, provides good to excellent yield without formation of any oxidized products of anilines or aldehydes and Schiff's bases as side products (table. III. B. 5).

Table. III. B. 5: Synthesis of 2, 4, 5-trisubstituted imidazoles using optimized reaction condition[a]:



Entry	R1	Product	Reaction time		Yield[b]	
			Benzil (min)	Benzoin (min)	Benzil (%)	Benzoin (%)
1			20	35	97	97

2			45	60	95	94
3			45	60	85	80
4			60	60	85	70
5			30	45	96	94
6			35	45	92	90
7			30	45	92	85
8			30	45	93	84
9			60	60	69	65
10			45	75	83	80

11			45	60	90	84
12			30	60	92	80
13			30	45	96	95
14			35	40	92	90
15 [c]			60	80	87	82
16 [d]			2 hrs.	2 ½ hrs.	> 20	> 15

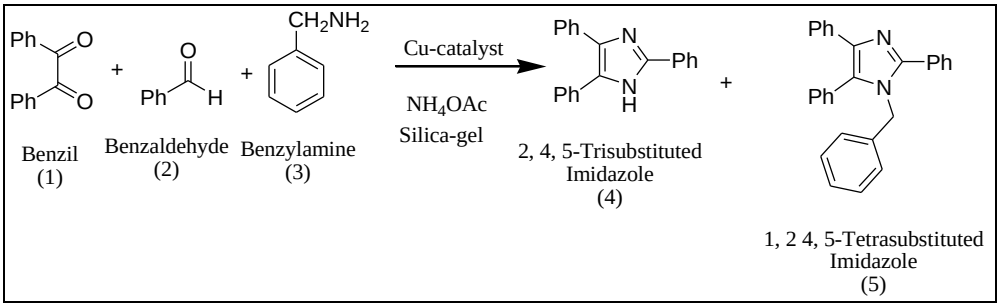
[a] reaction of benzil/benzoin (0.5 mmol), aldehydes (0.5mmol), NH_4OAc (1mmol), catalyst(2.5 mol%), silica-gel (750 mg) at 70^0C.

[b] all yields were isolated yield.[c] reaction temperature was 85^0 C.

[d] reaction temperature was varying from 70^0 to 90^0 C- no improvement of yield observed.

This observation persuades us to find whether the catalyst is equally applicable for the preparation of 1, 2, 4, 5-tetra substituted imidazole or not (scheme. III. B. 2). We started with benzil (1mmol), benzaldehyde (1nmol), benzyl amine (1mmol) and NH_4OAc (1 mmol) as a nitrogen source, silica-gel(1g) and the Cu-catalyst (10 mol%) at 70^0 C (scheme III. B. 2). We get a mixture of 2, 4, 5-tri substituted product and 1, 2, 4, 5-tetra substituted product (table. III. B. 6, entry 1). Further, to enhance the yield of the desired product, variations in the amount of catalyst,

benzyl amine and NH_4OAc and that of the temperature were attempted. But we failed to reach a satisfactory optimized reaction condition for the desired product.



Scheme III. B. 2. Preparation of 1, 2, 4, 5-tetrasubstituted imidazole

Table III. B. 6: Screening reaction condition for 1, 2 , 4, 5-Tetrasubstituted imidazole[a]:

Entry	NH_4OAc (mmol)	Benzyl amine (mmol)	Cu-catalyst (mol %)	Silica-gel (g)	Temp (^0C)	Time (h)	Yield(%)[b]	
							(4)	(5)
1[c]	1	1	10	1	60	4	65	25
2	–	–	–	–	70	5	80	15
3[d]	–	–	–	–	90	5	50	45
4[d]	–	–	–	–	120	$5^{1/2}$	55	35
5[e]	1.5	1.5	–	–	90	5	65	30
6[d, e]	1	1.5	–	–	90	$5^{1/2}$	45	40
8[f]	1	1	20	1	90	4	75	15

9 [g, h]	0.5	1.25	10	1	90	4	35	10

[a] reaction of benzil (1 mmol), benzaldehyde (1 mmol), Benzyl amine, NH_4OAc, Cu-catalyst and silica-gel [b]isolated yield
[c] got 3 % Schiff's base.
[d]no further change observed; monitoring by TLC, at same temperature
[e]no satisfied improvement of yield up to 120 ^{0} C
[f] reaction at higher temperature was not checked
[g]gives 40% Schiff's base at 90 ^{0} C
[h] mixture of products was obtained at 120 ^{0} C temp. : not isolated

III. B. 2. Experimental:

Scanning electron micrograph of the synthesized copper(II) complex have been analyzed using Inspect F-50 FEI scanning electron microscope with SEM accelerating voltage of 10.00 kV and magnification of 20000X. ^{1}H NMR and ^{13}C NMR were recorded on Bruker Advance FT-NMR (300 MHz) Spectrometer using TMS as internal standard.

III. B. 2. 1. Reaction procedure:

III. B. 2. 1. 1. General procedure for the preparation of Cu II-Catalyst:

A mixture of 3,5-dinitrobenzoic acid (0.1688 g), $Cu(NO_3)_2.3H_2O$ (0.1932 g) and melamine (0.1002 g) was taken and grind to dust in a mortar pistol. To the mixture 1.5 mL of distilled water was added and stirred for 30m until we get a suspension. Then the reaction mixture was sealed in a 10 ml Teflon-lined stainless-steel autoclave and heated for 45 h at 423 K. After that the autoclave was subjected to cooling (for 5 h) to room temperature. The reaction mixture was filtered and was subsequently wash with distilled water. We get blue colored crystal of the product, which we take for further characterization by single crystal X-ray diffraction, SEM.

III. B. 2. 1. 2. General Process for the preparation of 2, 4, 5-tri substituted imidazole:

A mixture of Benzil (0.5 mmol.), ammonium acetate (1 mmol), aldehydes (0.5 mmol) and Cu-catalyst (2.5 mol %) was added with silica gel (for TLC, 750 mg) and grind well. The mixture was taken in a50mL round bottom flask and heated in an oil bath at 70^{0}C with proper stirring on magnetic stirrer for specified time (table. III. B. 5). The progress of reaction was monitored by TLC. After the completion of the reaction the product was extracted with Ethyl acetate and

further purified by Column Chromatography using silica gel 60-120 mesh. Solid product obtained from column chromatography was recrystallized using ethyl acetate and pet ether (9:1).

III. B. 2. 1. 3. Recycling of Catalyst over silica-gel:

For reusability test of catalyst on silicagel, we washed catalyst loaded on silica-gel with dry methanol (3x15 mL) and distilled water (3x15 mL) after extracting the product with ethyl acetate at completion of reaction after every run. Then catalyst with silica-gel was dried up with the help of reduced pressure for overnight and used for reactions.

III. B. 2. 2. Chemicals:

All the chemicals used in this investigation including their purity and sources are summarized in the following table (table. III. B. 7).

Table III. B. 7. Chemicals used for present investigation:

Entry	Chemical	Sources	Purity (%)
1	Benzaldehyde	SRL	99
2	3-Methoxybenzaldehyde	Chemical Book	97
3	2-Hydroxybenzaldehyde	S.D. Fine	99
4	4-Methoxybenzaldehyde	Sigma-Aldrich	98
5	4- (N, N-Dimethyl amino) benzaldehyde	Sigma-Aldrich	99
6	4- Nitro benzaldehyde	LOBA chemie	98
7	4-Hydroxy benzaldehyde	S.D. Fine	98
8	2-Hydroxy-3-methoxy benzaldehyde	ACROS	99
9	4-Hydroxy-3-methoxy benzaldehyde	S.D. Fine	99
10	3-Nitro benzaldehyde	LOBA chemie	98
11	2-Npthaldehyde	Sigma-Aldrich	98
12	1-Napthaldehyde	Sigma-Aldrich	95

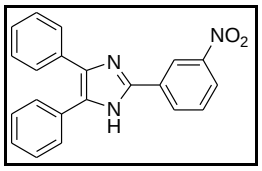
13	2-Chloro benzaldehyde	S.D. Fine	99
14	Furfural	Sigma-Aldrich	99
15	4-fluoro benzaldehyde	Spectrochem	97
16	4-methoxypyridine-2- carbaldehyde	Sigma-Aldrich	96
17	Thiophene- 2-carbaldehyde	Sigma-Aldrich	98
18	DMSO-$d_6$for NMR	S.D. Fine	97
19	Petroleum ether	Thomas Baker	98
20	Ethyl acetate	Thomas Baker	99
21	Silica-gel 60-120 mesh for column	SRL	-
22	Silica-gel for TLC	SRL	-
23	Na_2SO_4anhydrous	SRL	99.5
24	Benzil	SRL	98
25	3,5-Dinitrobenzoic acid	Sigma-Aldrich	99
26	$Cu(NO_3)_2.3H_2O$	SRL	99.5
27	Melamine	Sigma-Aldrich	99

III. B. 3. Conclusion:

By the above investigation we concluded that Poly [(μ_3-3,5-dinitrobenzoatok^3 O^1:$O^{1'}$:O^3) (µ2-hydroxido-k^{2}O:O)-copper(II)] (Fig. 1a) can act as an inexpensive, non-toxic and reusable catalyst for preparation of 2,4,5-tri substituted imidazoles using benzil, aldehydes, ammonium acetate under solvent free reaction condition. Hence our recent methodology can provide a more atom economic and environment friendly, i.e. greener way than the existing conventional methods.

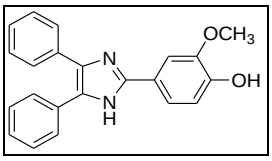
III. B. 4. Spectroscopic data of synthesized compounds:

III. B. 4. 1. 2-(3-nitrophenyl)-4, 5-diphenyl-1*H*-imidazole:



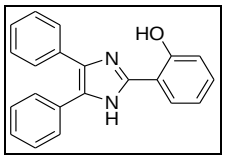
M.P. 267-269^{0}C; ^{1}H NMR (300 MHz, DMSO-d_6): δ, 7.70-7.23 (m, 10H),7.78 (t, 1H, J=7.8 Hz),8.20-8.23(m, 1H),8.52 (dd, 1H, J=6.9, 8.7, Hz),8.96 (s, 1H), 13.11(s, 1H)ppm.^{13}C NMR (75 MHz, DMSO-d_6): δ, 119.9, 123.0, 127.2, 127.6, 128.5, 128.7, 128.9, 129.1, 130.8, 131.1, 131.6, 132.3, 135.2, 138.2, 143.8, 148.9 ppm.

III. B. 4. 2. 2-(4-hydroxy-3-methoxyphenyl)-4, 5-diphenyl-1*H*-imidazole:



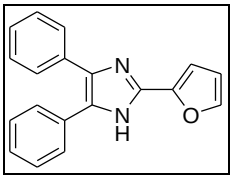
M.P. 221-224^{0}C; ^{1}H NMR (300 MHz, DMSO-d_6): δ, 3.86 (s, 3H), 7.65-7.36 (m, 12H), 6.87 (d, 1H, J=8.1Hz), 9.82 (s, 1H), 12.43(s, 1H) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ, 56.2, 109.9, 116.1, 118.9, 122.4, 127.7, 128.8, 146.5, 147.5, 148.2 ppm.

III. B. 4. 3. 2-(2-hydroxyphenyl)-4, 5-diphenyl-1*H*-imidazole:



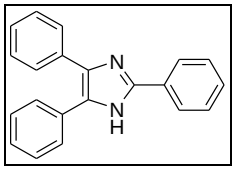
M.P. 202-204^{0}C; ^{1}H NMR (300 MHz, DMSO-d_6): δ, 6.93 -7.53 (m, 13H), 8.05 (d, 1H, J=7.2Hz),12.97 (s, 1H), 13.059 (s, 1H)ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ, 113.3, 117.3, 119.3, 125.4, 127.2, 127.5, 128.8, 128.9, 129.2, 130.6, 134.0, 134.6, 146.3, 157.1 ppm.

III. B. 4. 4. 2-(furan-2-yl)-4, 5-diphenyl-1*H*-imidazole:



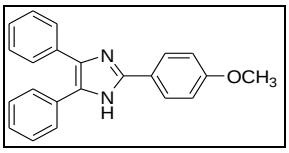
M.P. 214-215^{0}C; ^{1}H NMR (300 MHz, DMSO-d_6): δ, 6.65 (s, 1H), 6.99 (s, 1H), 7.31-7.98 (m, 11H), 12.84 (b, 1H) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ, 107.9, 112.3, 128.2, 128.9, 139.0, 143.5, 146.1 ppm.

III. B. 4. 5. 2, 4, 5-triphenyl-1*H*-imidazole:



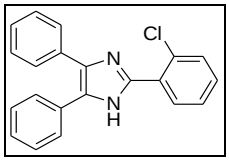
M.P. 270-272^{0}C; ^{1}H NMR (300 MHz, DMSO-d_6): δ, 7.20-7.55 (m, 15 H), 12.68 (s, 1H) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ, 125.6, 126.9, 127.5, 128.7, 128.9, 129.1, 130.8, 135.6, 137.6, 145.9 ppm.

III. B. 4. 6. 2-(4-methoxyphenyl)-4, 5-diphenyl-1*H*-imidazole:



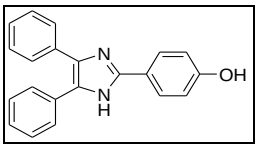
M.P. 224-227^0 C; ^{1}H NMR (300 MHz, DMSO-d_6): δ, 3.74 (s, 3H), 7.03 (d, 2H, J=8.7 Hz), 7.22-7.94 (m, 10 H), 8.01 (d, 2H, J=8.7 Hz), 12.51(s, 1H) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ, 56.7, 114.5, 123.6, 126.9, 127.2, 127.5, 128.1, 128.7, 128.8, 129.1, 146.1, 159.9 ppm.

III. B. 4. 7. 2-(2chlorophenyl)-4, 5-diphenyl-1*H*-imidazole:



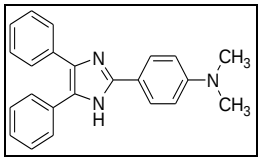
M.P. 224-227^0 C; ^{1}H NMR (300 MHz, DMSO-d_6): δ, 7.13-7.54(m, 13H), 7.72-7.74 (m, 1H), 12.58(s, 1H) ppm.^{13}C NMR (75 MHz, DMSO-d_6): δ, 127.0, 127.6, 128.2, 128.5, 128.6, 128.7, 129.1, 130.5, 130.6, 131.4, 131.9, 132.1, 135.6, 137.4, 143.9 ppm.

III. B. 4. 8. 2-(4hydroxyphenyl)-4, 5-diphenyl-1*H*-imidazole:



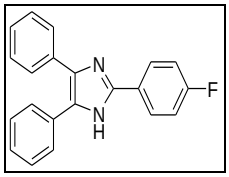
M.P. 268-271^0 C; ^{1}H NMR (300 MHz, DMSO-d_6):δ, 6.85 (d, 2H, J= 4.5Hz), 6.86-7.91 (m, 10 H), 7.93 (d, 1H, J= 4.2Hz), 9.74(s, 1H), 12.43(s, 1H) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ, 115.9, 122.1, 126.8, 127.3, 127.5, 127.9, 128.7, 129.0, 146.5, 158.2 ppm.

III. B. 4. 9. 2-(4-Dimethylaminophenyl)-4, 5-diphenyl-1*H*-imidazole:



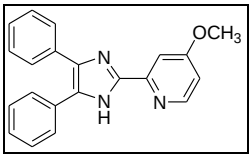
^{1}H NMR (300 MHz, DMSO-d_6): δ, 2.97 (s, 6H), 6.76 (md 2H, J= 8.7 Hz), 7.27-7.51 (m,10H), 7.90 (d, 2H, J= 8.7 Hz), 12.34 (b,1H) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ, 40.4, 112.4, 118.8, 126.8, 127.3, 128.1, 128.8, 146.9, 150.7 ppm.

III. B. 4. 10. 2-(4-fluorophenyl)-4, 5-diphenyl-1*H*-imidazole:



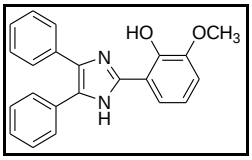
^{1}H NMR (300 MHz, DMSO-d_6): δ, 7.22-7.56 (m, 12H), 8.09 (d, 2H, J=7.2 Hz), 12.69(s, 1H) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ, 125.7, 126.9, 127.5, 127.9, 128.2, 128.6, 128.7, 128.8, 128.9, 129.1, 130.0, 130.8, 131.6, 133.0, 135.7, 137.6, 145.9 ppm.

III. B. 4. 11. 2-(4-methoxypyridine-2-yl)-4, 5-diphenyl-1*H*-imidazole:



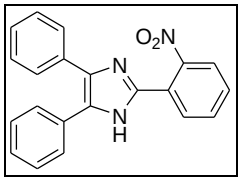
M.P: 206-209^{0} C;^{1}H NMR (300 MHz, DMSO-d_6):δ, 12.50(s, 1H) ppm.^{13}C NMR (75 MHz, DMSO-d_6): δ, 56.7, 114.6, 123.6, 126.9, 127.2, 127.5, 128.1, 128.6, 128.8, 129.1, 137.2, 146.1, 159.9 ppm.

III. B. 4. 12. 2-(2-hydroxy-3-methoxyphenyl)-4, 5-diphenyl-1*H*-imidazole:



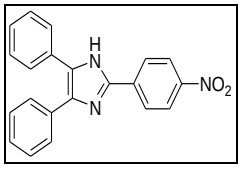
^{1}H NMR (300 MHz, DMSO-d_6): δ, 3.82 (s, 3H), 4.05(s, 1H), 6.88 (t, 1H, J= 7.8 Hz), 6.98 (d, 1H, J= 8.1Hz), 7.28-7.52 (m, 10 H), 7.66 (d, 1 H, J= 7.8 Hz), 13.04(s, 1H) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ, 56.1, 113.1, 113.3, 117.2, 118.9, 127.3, 127.6, 129.0, 129.3, 130.7, 134.0, 146.5, 147.3, 148.8 ppm.

III. B. 4. 13. 2-(2-nitrophenyl)-4, 5-diphenyl-1*H*-imidazole:



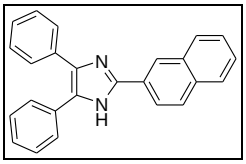
M.P 230-232^0 C; ^{1}H NMR (300 MHz, DMSO-d_6): δ, 7.26-7.56 (m, 10 H), 7.67(t, 1H, J=7.8 Hz), 7.81 (t, 1H, J=7.5 Hz), 7.96 (d, 1H, J=7.8 Hz), 8.04(d, 1H, J=7.8 Hz), 13.01(s, 1H) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ, 123.9, 124.4, 127.2, 127.4, 128.5, 128.7, 129.2, 130.0, 131.1, 132.6, 135.2, 138.0, 141.5, 148.8 ppm.

III. B. 4. 14. 2-(4-Nitrophenyl)-4, 5-diphenyl-1*H*-imidazole:



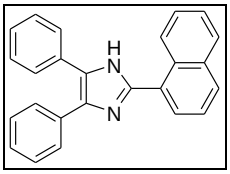
M.P. 192-194^{0}C; ^{1}H NMR (300MHz, DMSO-d_6): δ, 7.25-8.43 (m, 14H), 12.59 (s, 1H) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ, 123.2, 126.7, 126.9, 131.8, 147.3, 159.8 ppm.

III. B. 4. 15. 2-(2-Napthyl)-4, 5-diphenyl-1*H*-imidazole:



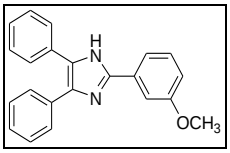
M.P. 270-273^o C; ^{1}H NMR (300 MHz, DMSO-d_6): δ, 7.24-7.59 (m, 13H), 7.93-8.02 (m, 3H), 8.26 (dd, 1H, J=1.5, 8.4Hz), 8.61 (s, 1H), 12.89 (s, 1H) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ, 123.9, 124.1, 126.8, 127.1, 127.2, 127.6, 128.2, 128.3, 128.5, 128.7, 128.8, 129, 129.1, 131.4, 133.1, 133.4, 135.5, 137.8, 145.1 ppm.

III. B. 4. 16. 2-(Napthalen-1-yl)-4,5-diphenyl-1*H*-imidazole:



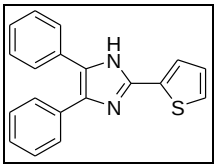
M.P. 266-268^{0}C^{1}H NMR (300 MHz, DMSO-d_6): δ, 7.25-8.03 (m, 17H), 12.09 (s, 1H) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ, 125.2, 126.1, 127.2, 127.4, 127.6, 128.2, 128.6, 129.1, 129.3, 129.8, 130.0, 130.1, 133.3, 133.6, 145.5 ppm.

III. B. 4. 17. 2-(3-Methoxyphenyl)-4, 5-diphenyl-1*H*-imidazole:



M.P. 262-264^{o}C; ^{1}H NMR (300 MHz, DMSO-d_6): δ, 3.84 (s, 3H), 6.83-7.84 (m, 14H), 12.61 (s, 1H) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ, 55.6, 110.4, 113.9, 117.8, 127.8, 128.2, 128.5, 128.6, 128.7, 128.8, 129.1, 135.3, 145.6, 159.4 ppm.

III. B. 4. 18. 4, 5-Diphenyl-2-(thiophen-2-yl)-1*H*-imidazole:



M.P. 261-263^0 C; ^{1}H NMR (300 MHz, DMSO-d_6): δ, 7.14-7.80 (m, 11H), 7.93 (d, 1H, J=7.2Hz), 12.76 (b, 1H) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ, 126.9, 128.2, 128.4, 134.8, 139.1, 142.0 ppm.

III. B. 5. Supporting Spectra:

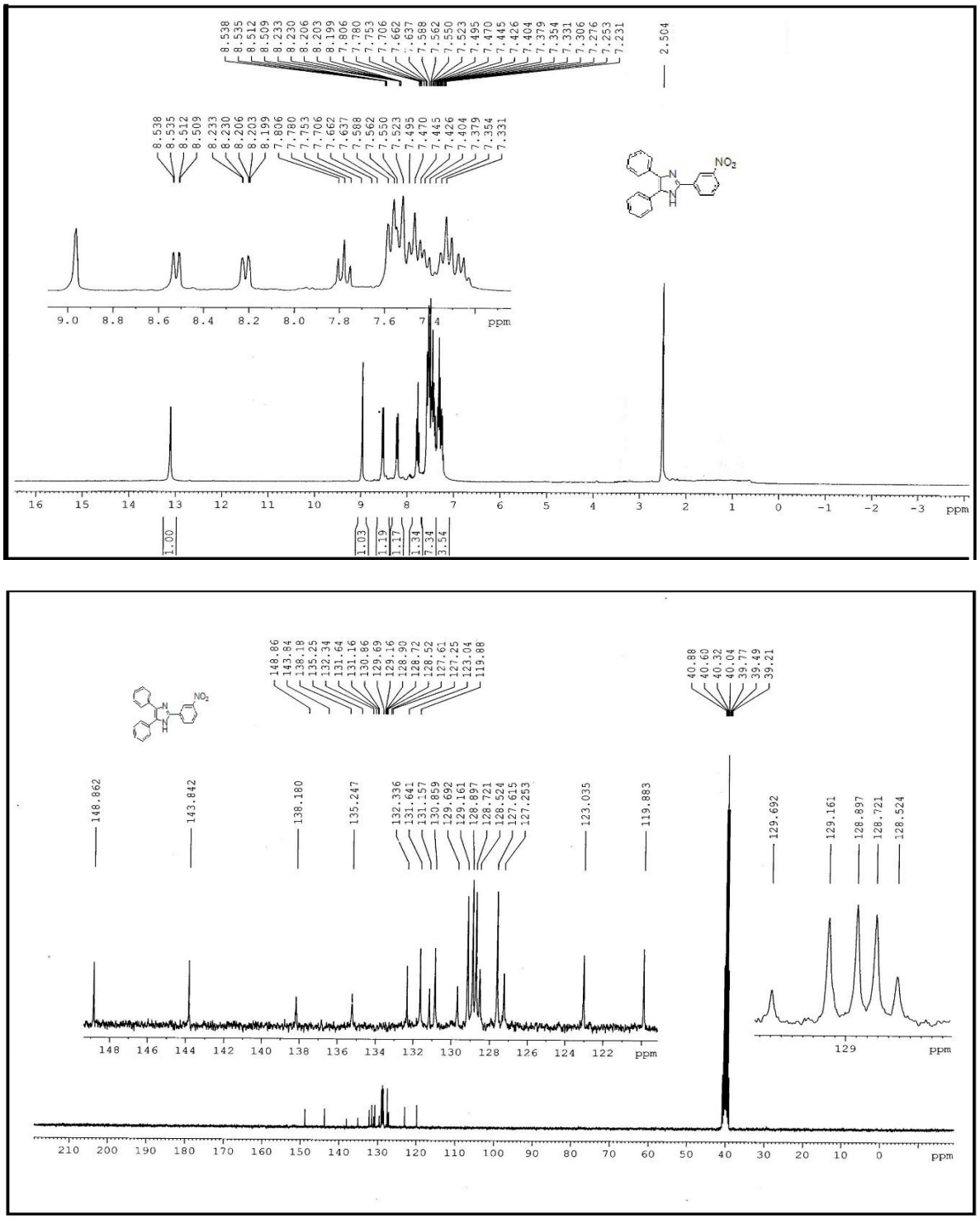


Fig. III. B. 5. ^{1}H and ^{13}C NMR of 2-(3-nitrophenyl)- 4, 5-diphenyl-1*H*-imidazole.

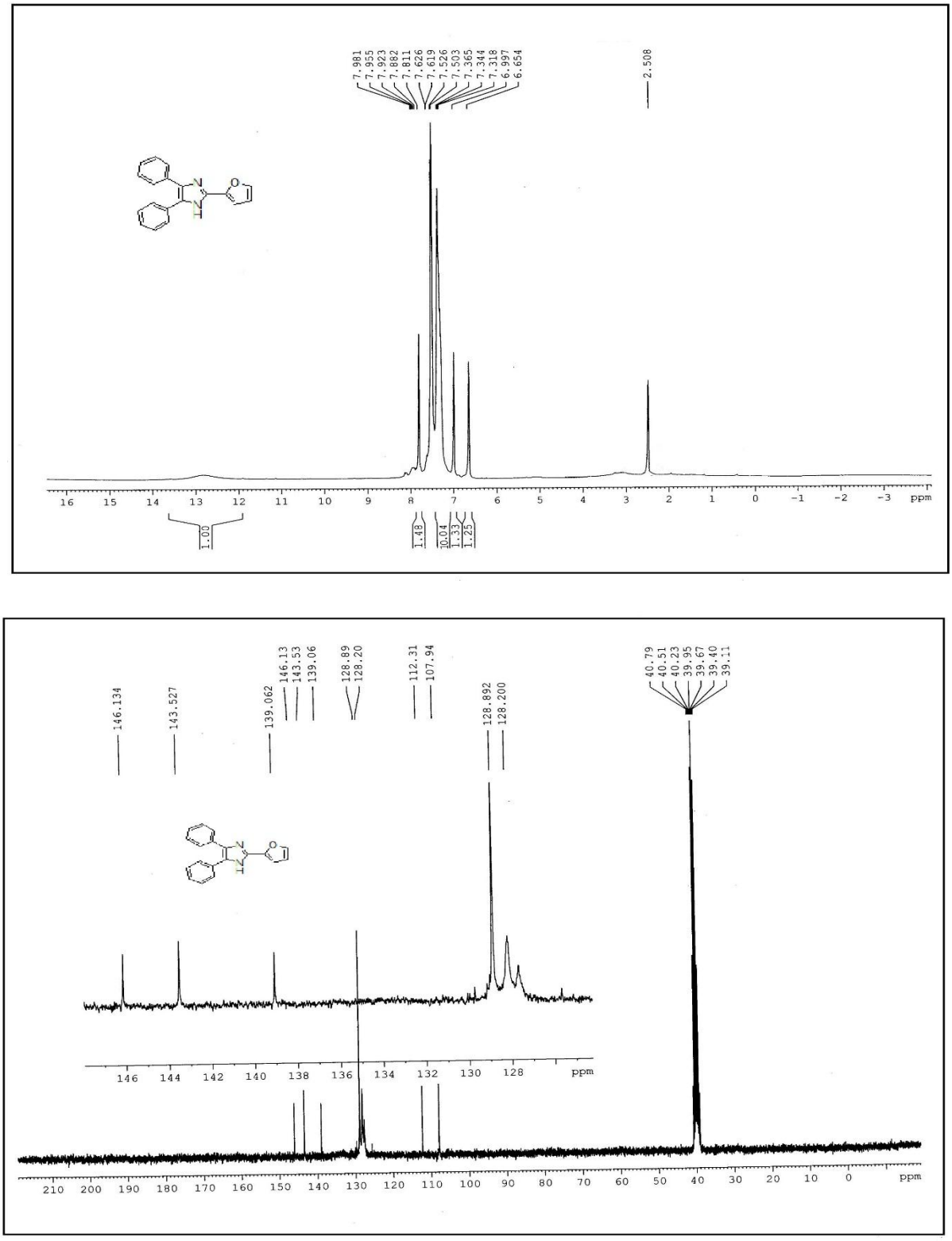


Fig. III. B. 6. ^{1}H and ^{13}C NMR of 2-(furan-2-yl)-4, 5-diphenyl-1*H*-imidazole

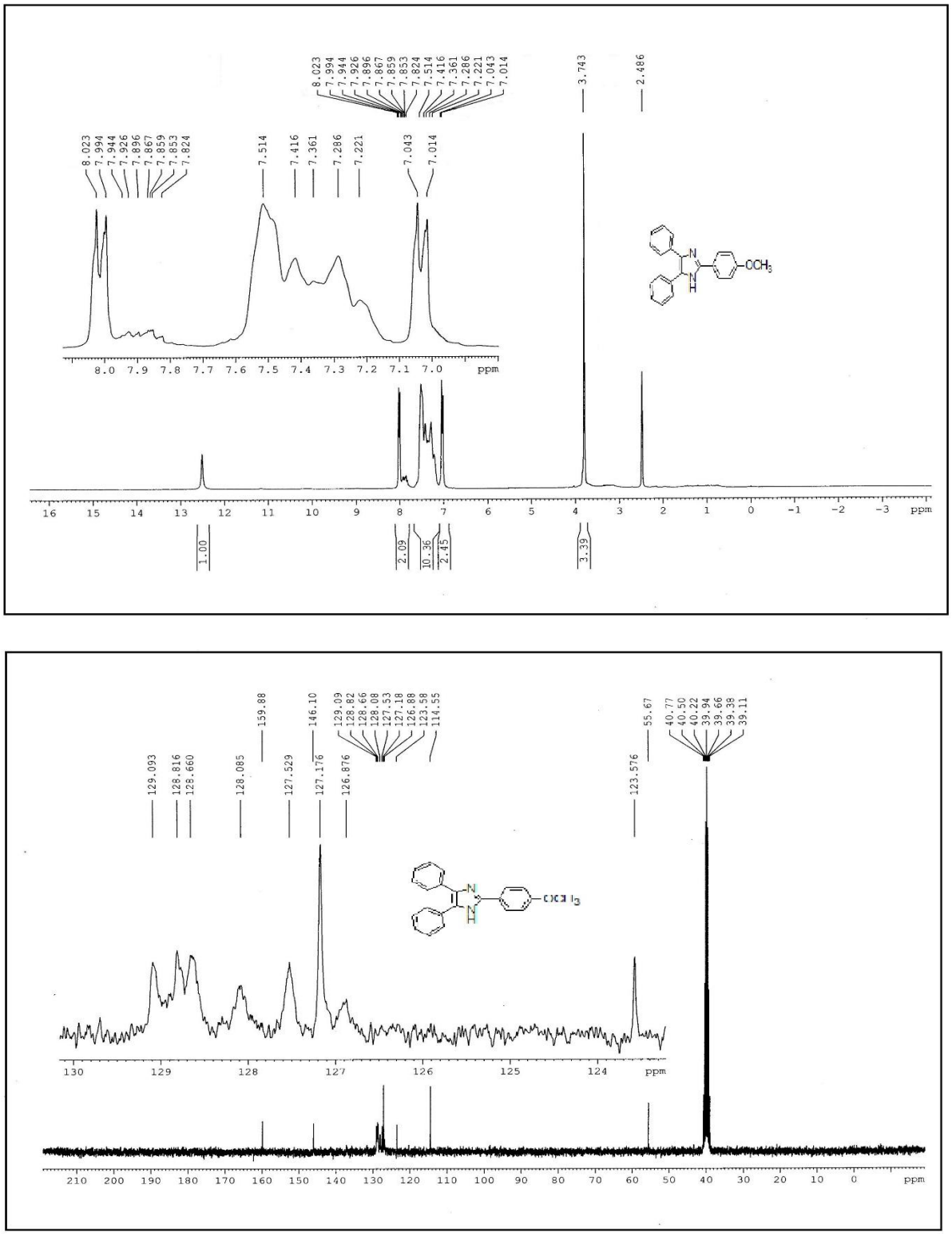


Fig. III. B. 7. ^{1}H and ^{13}C NMR of 2-(4-methoxyphenyl)-4, 5-diphenyl-1*H*-imidazole

Chapter IV

Highly efficient polymeric-Cu (II) catalysed one pot multi-component synthesis of substituted N-heterocycles *via* double condensation/ tandem oxidation-cyclisation/elimination cyclisation reactions from diverse starting precursors under milder reaction conditions:

Section A

(General introduction and synthetic background)

IV. A. 1. A general introduction of pyrazine and quinoxaline and their synthetic background:

Pyrazine is an organic heterocyclic compound having molecular formula $C_4H_4N_2$. Structurally pyrazine hasa symmetrical moiety, with two nitrogen atoms at 1 and 4 positions respectively in a benzene ring (fig. IV. A. 1). They are important components of aroma fragrances and naturally found in fenugreek.

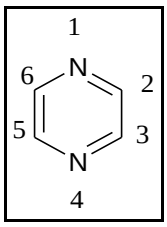


Fig. IV. A. 1. General structure of pyrazine moiety

Whereas quinoxaline has molecular formula $C_8H_6N_2$ and formed by the fusion of two aromatic rings benzene and pyrazine, hence they are also known as benzopyrazine. In quinoxaline two nitrogen atoms are present at 1 and 4 positions of a naphthalene ring (fig. IV. A. 2). It is an important class of biologically active moiety and acts as bioisoster of benzo-thiophene, naphthalene and quinoline.

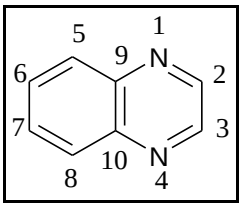


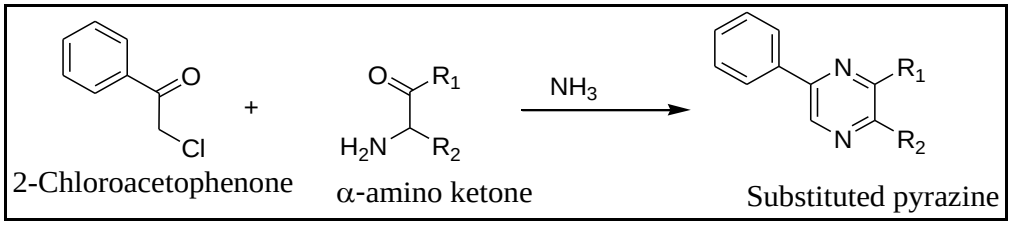
Fig. IV. A. 2. Quinoxaline moiety

IV. A. 2. Methods of preparation of pyrazine and quinoxaline:

There are a number of classical and modern methods for the synthesis of both pyrazine and quinoxaline from diverse precursor are available. Some of them are described below.

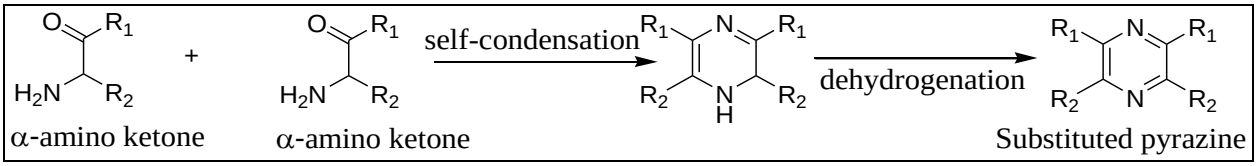
IV. A. 2. 1. Classical methods for pyrazine synthesis:

Classically, pyrazine was synthesized by the condensation- oxidation of 2-chloroacetophenone with α-amino ketone in presence of ammonia, given by Staedel–Rugheimer in 1876 (scheme. IV. A. 1).



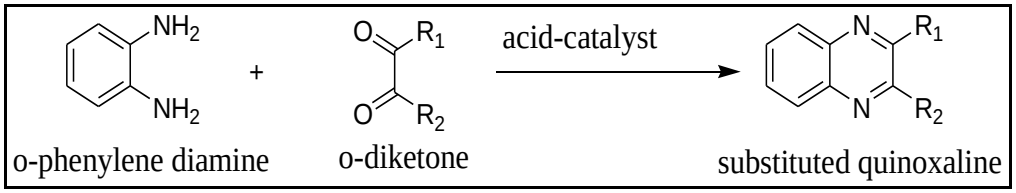
Scheme. IV. A. 1. Staedel–Rugheimer pyrazine synthesis.

Moreover, due to presence of lachrymatory agent 2-chloroacetophenone, Gutknecht in 1879 modified the technique in which self-condensation of α-amino ketones are takes place followed by dehydrogenation (scheme. IV. A. 2).



Scheme. IV. A. 2. Gutknecht process of pyrazine synthesis.

Similarly, quinoxaline is prepared by the condensation of α- dicarbonyl compounds with o-phenylene diamine in presence of an acid catalyst (scheme. IV. A. 3).



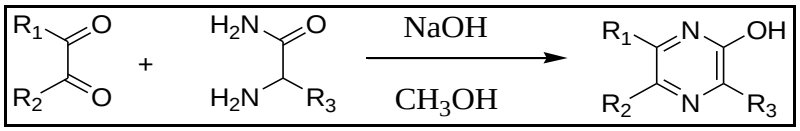
Scheme. IV. A. 3. Classical method of quinoxaline preparation

IV. A. 2. 2. Modern method of pyrazine and quinoxaline preparation:

As the classical route for preparation of pyrazine and quinoxaline gives quite satisfactory yield, but long reaction time, strong acidic medium and high temperature make the necessity to find a milder and acceptable method for their preparation. Literature survey reveals a numerous method for synthesis of pyrazine and quinoxaline.

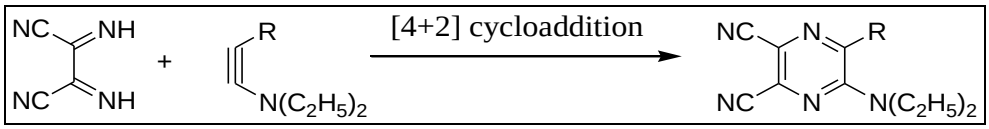
IV. A. 2. 2. 1. Modern method of pyrazine synthesis:

Since the method developed by Staedel–Rugheimer in 1876 a number of alternatives are reported for synthesis of pyrazine and their derivative using different precursor to achieve a milder reaction condition. Such as R.G. Jones in 1949 reported the condensation of α-amino acid amides and 1,2-dicarbonyl in presence of sodium hydroxide in methanol (scheme. IV. A. 4) [1].



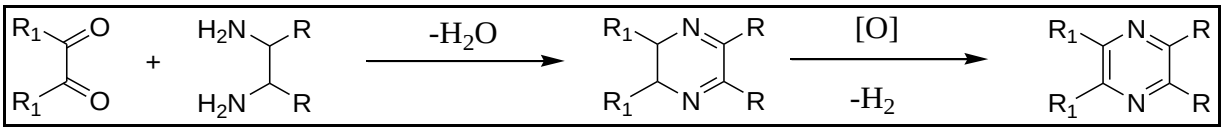
Scheme. IV. A. 4. Jones method of pyrazine synthesis

E.C. Taylor et.al, in 1959 reported the pyrazine synthesis by condensation of α, β-dicarbonyl and amino malonamidamidine in presence of dilute NH_4OH at 0-20 ^0C [2]. Later, Ohtsuka et. al. in 1979 reported the cyclisation of 2,3-bis (arylidene amino)-3- cyano arylamides followed by oxidation produced corresponding pyrazine [3]. Again, in 1981 E.C. Taylor et.al synthesized pyrazine derivative by reaction of 3,3-dimethoxy-1-(pyrrolidin-1- yl) prop-1-en-2-yl) carbonimidoyl dicyanide and ammonia in MeOH solution [4]. Fukunaga et. al. prepared pyrazine derivative by [4+2] cycloaddition reaction between yn-amines and 1,2-dimethoxyethylene (scheme. IV. A. 5) [5].



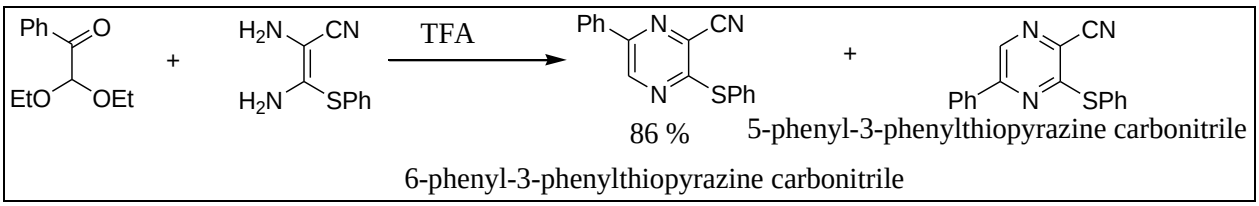
Scheme. IV. A. 5. [4+2] cycloaddition reaction for pyrazine synthesis

Later, Buechi et. al. in 1991 provided the regioselective formation of alkyl pyrazine by the condensation of α-oximido carbonyl and allyl amines [6]. In 1997 T. L. Gilchrist reported the preparation of pyrazine through the formation of dihydro pyrazine followed by oxidation using 1, 2- diaminoethane and 1, 2-dicabonyl (scheme. IV. A. 6) [7].



Scheme. IV. A. 6. Gilchrist pyrazine synthesis

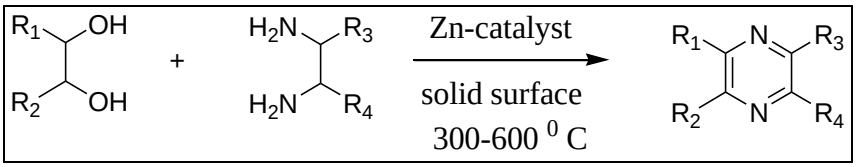
In, 2001 W. Zhang et al. synthesized a pyrazine derivative 6-phenyl-3-phenylthiopyrazine carbonitrile selectively using 2, 3- diamiono-3-phenylthio-acrylonitrile and 2,2-diethoxy acetophenone in excess TFA (scheme. IV. A. 7) [8].



Scheme. IV. A. 7. Selective synthesis of 6-phenyl-3-phenylthiopyrazine carbonitrile

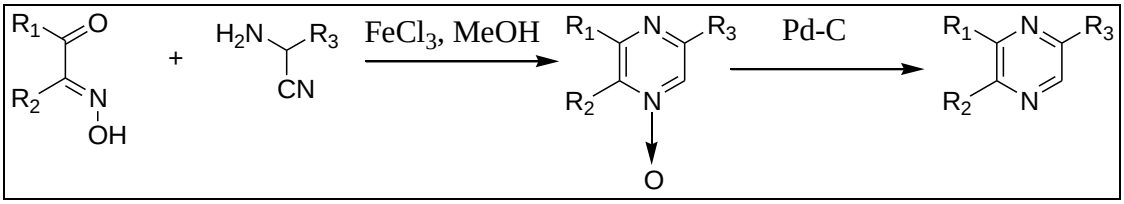
This synthetic approach further continued as a method of options to prepare pyrazine and its derivative among the chemist (e.g. ortho linked oxacalix-[2]-benzene-[2]-pyrazine prepared by L. W. Kong et al) [9].

Besides these metal free catalytic approaches, a number of methods using metal catalyst for pyrazine synthesis are also reported. Such as Anderson et al. in 1967 reported deamination of diethylenetriamine a mixture of catalyst Mo_2O_3: P_2O_5: Al_2O_3 (in ratio 5:1:94) to produced pyrazine derivative [10]. J. Okada in 1974 reported the condensation of diamines with diol in presence of granular alumina in vapour phase for the first time [11]. Sato in 1978 reported pyrazine preparation by reaction of diamine and diol in presence of Zinc catalyst at 300-600 ^{0}C over solid surface such as silica or alumina or silica-alumina (scheme. IV. A. 8) [12].



Scheme. IV. A. 8. Formation of pyrazine using Zn-catalyst

Further, Lee et al. prepared pyrazine using copper-chromite catalyst [13]. In 2002 Itoh et al. reported preparation of pyrazine through the synthesis of pyrazine-N-oxide by reaction of iso-nitroso acetophenone and aminoacetonitrile using $FeCl_3$ as a catalyst followed by subsequent reduction by Pd-C (scheme. IV. A. 9) [14].

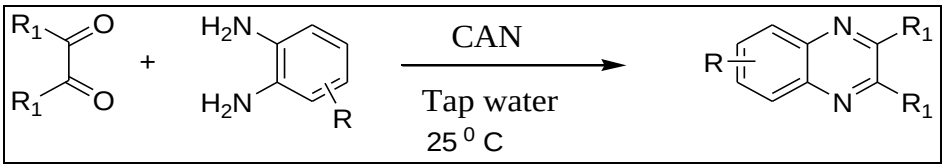


Scheme. IV. A. 9. Itoh et al. process for pyrazine synthesis.

In 2003 Raw et al. reported the reaction of α-hydroxyl ketones and 1,2- diamines in KOH-MeOH using MnO_2 as a catalyst to prepared pyrazine [15]. Later, Park et al. prepared methyl pyrazine by reaction of ethylenediamine and propylene glycol using $CuO\text{-}ZnO\text{-}SiO_2$ as a catalyst [16]. Moreover, Latha et al. reported preparation of pyrazine selectively from ethylenediamine using copper oxide-copper chromite catalyst [17] and also Ghosh et al has reported the greener protocol for pyrazine synthesis [18].

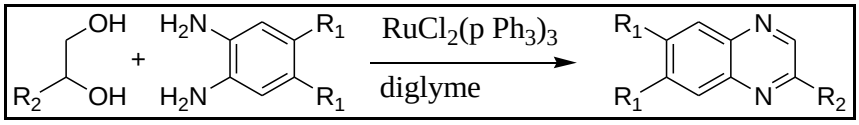
IV. A. 2. 2. 2. Modern method of preparation of quinoxaline:

As the classical method for quinoxaline preparation required strong acidic medium, a more suitable and acceptable method is a basic concern for modern synthetic chemist. Recently literature survey reveals a number of methods for the synthesis using different precursor. Basically, reaction of *vic*-diketo with *vic*-diamines using different catalyst is the most straight forward method (e.g. More et al. recently reported cerium (IV) ammonium nitrate catalysed synthesis of quinoxaline derivative, scheme. IV. A. 10) [19].



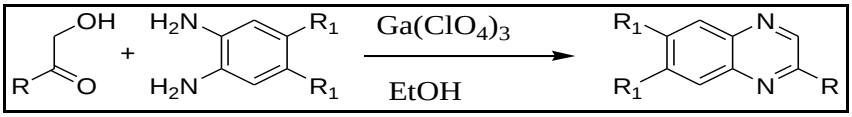
Scheme. IV. A. 10. CAN catalyse quinoxaline synthesis

Again, Esmaeilpour et al. used Fe_3O_4@SiO_2/ Schiff base complex nano particle as their potent catalyst [20] and Brahmachari et al. took magnetically separable $MnFe_2O_4$ as a catalyst [21]. There also certain other precursors are used for quinoxalines synthesis. Such as: *vic*-diol as reported by Cho et al. during their synthesis of quinoxaline by the reaction of substituted *o*-phenylene diamines and *vic*-diols using ruthenium complex as a catalyst; scheme. IV. A. 11). [22]



Scheme. IV. A. 11. Ruthenium catalysed quinoxaline synthesis from *vic*-diol.

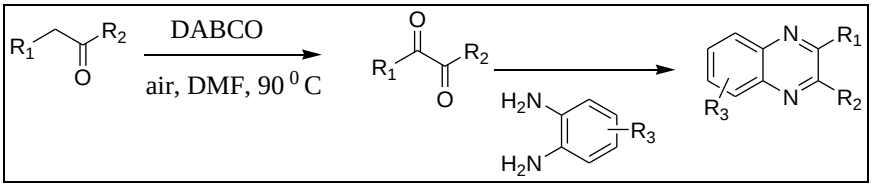
Moreover, α-arylimino oxime (e.g. Xekoukoulotakis et al. reported the cyclisation of α-arylimino oxime in presence of acetic acid under reflux condition for quinoxaline synthesis) [23], α-diazoketones (as reported by Yadav et al. reported cyclisation of α-diazoketones and 1,2-diamine using $Cu(OTf)_2$ as potent catalyst [24]) and α-hydroxy ketones (e.g. Pan et al. synthesized quinoxaline by cycloaddition of α-hydroxy ketones with o-phenylene diamines using $Ga(ClO_4)_3$ as a catalyst, scheme. IV. A. 12 [25]; again, Sithambaram et al. used manganese octahedral molecular sieves as their potent catalyst for the tandem process [26]) are also used as a precursor.



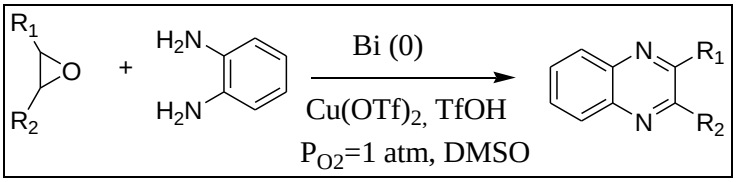
Scheme. IV. A. 12. Quinoxaline synthesis via cyclisation of *α*-hydroxy ketones and *o*-phenylene diamines

Again, deoxy-benzoin (e.g. Qi et al. described the DABCO catalysed in-situ oxidation followed by cyclization of deoxy-benzoin with aryl-1, 2-diamine to quinoxaline, scheme IV. A. 13) [27], epoxide (e.g. Antoniotti et al. gave the Bi(0) catalysed synthesis of quinoxaline from epoxide and

ene- 1,2-di amine using $Cu(OTf)_2$ and TfOH as additive in DMSO solvent, scheme. IV. A. 14) [28], 1,2-Diaza-1,3-butadienes (such as, Aparicio et al. describe the direct synthesis of quinoxaline from 1,2-Diaza-1,3-butadienes by reaction with 1,2-iamines) [29], nitroolefins (e.g. Chen et al. reported quinoxaline synthesis by reaction of nitroolefins with *o*-phenylene diamines using $CuBr_2$ as a catalyst) [30],*o*-alkynyl aldehydes (e.g. Rustagi et al. reported regioselective tandem reaction for quinoxaline synthesis from *o*-alkynyl aldehydes using Ag(I) salt as a catalyst) [31], alkynes (Wnag et al. reported Cu catalysed synthesis of quinoxaline using *o*-phenylene diamines and terminal alkynes in presence of bases) [32], phenacyl bromide (e.g. DABCO catalysed quinoxaline preparation by phenacyl bromide and aryl-1,2-diamine via cyclization-oxidation process) [33] are also used rather than the reactive 1,2-diketo compounds.



Scheme. IV. A. 13. DABCO catalysed oxidation-cyclisation reaction for quinoxaline synthesis.



Scheme. IV. A. 14. Bi (0) catalysed quinoxaline preparation from epoxide.

Other elegant methods comprise with: reaction of 2-nitro aniline with *vic*- diol by hydrogen transfer (e.g. ruthenium catalysed hydrogen transfer technique for quinoxaline synthesis reported by Xie et al.) [34], reaction of polymer linked *o*-Nitrophenyl carbamate with *α*-bromo ketone *via* sequential reductive coupling and cyclisation reported by Singh et al. [35], microwave-irradiation technique (e.g. Zhou et al. reported catalyst free synthesis of quinoxaline derivative by microwave irradiation, [36] and via benzyne intermediate formation on solid phase as reported by Dixon et al.[37] are also been reported with varied success.

IV. A. 3. Conclusion:

Although, variety of methods are available for the synthesis of both pyrazine and quinoxaline, most of them are limited by harsh reaction condition, long reaction time, tedious work-up procedure, use of toxic solvent or heavy metal catalyst and also for poor yield. These drawbacks motivate the author of this thesis for the development of a milder, efficient and environmentally being method for their synthesis pyrazine and quinoxaline moieties.

Chapter IV

Section B

(Present investigation)

Highly efficient polymeric-Cu (II) catalysed one pot multi-component synthesis of substituted N-heterocycles *via* double condensation/ tandem oxidation-cyclisation/elimination-cyclisation reactions from diverse conventional starting precursors under milder reaction conditions:

IV. B. 1. Result and Discussion:

Initially, effort was focused on the evaluation of catalytic activity of our prepared Cu (II)-catalyst (fig. IV. B. 1), which was characterized by mass, XRD and SEM images (details were already discussed in the experimental section of chapter 3 section- B) for the synthesis of pyrazine using benzil and ehane-1,2-diamime as our primary precursor (scheme. IV. B. 1). We mixed benzil (1 mmol), ethane-1, 2-diamine (1 mmol) and Cu- catalyst (10 mol %) in methanol (3 mL) and stirred at room temperature for overnight. An acceptable yield (89 %) of the desired product (2, 3-diphenylpyrazine) encourages us for further investigation our reaction protocol. On, the observation of the progress of reaction, using different solvents and under various reaction conditions (table. IV. B. 1), we detect dihydro pyrazine along with pyrazine at the early stages of reaction (entry 2 and 3 of table. IV. B. 1). This result suggests a simple in situ aromatization of dihydro pyrazine to pyrazine without any additional step as was reported in the literature. On further screening of reaction condition, we reached ouroptimized reaction condition as benzil (1 mmol), ethane-1, 2-diamine (1 mmol), catalyst (5 mol %) and methanol (3mL) at 50 ^{0} C (entry. 12 of table. IV. B. 1). Further decline the amount of catalyst cause a drastic fall in the yield of product formation (entry 14-18 of table. IV. B. 1).

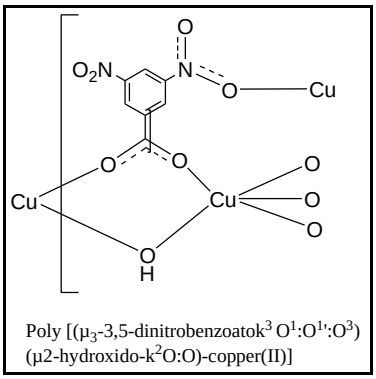
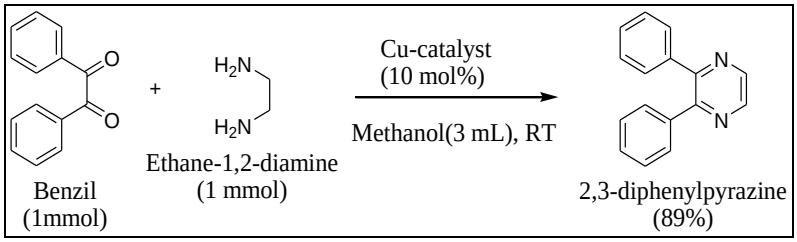


Fig. IV. B. 1: General structure of the prepared polymeric Cu (II)-complex catalyst.



Scheme. IV. B. 1. Cu (II)-catalysed double condensation of benzil and etane-1, 2-diamine.

Table. IV. B. 1: Optimization of reaction condition [a]:

Entry	Catalyst (mol %)	Solvent (mL)	Temp (^{0}C)	Time (h)	Yield (%)[b]
1[c]	10	Methanol	Room temp.	12	89
2[d]	-	-	-	3	57
3[d]	-	-	-	6	75
4[e]	-	-	-	9	89
5	5	-	-	12	89

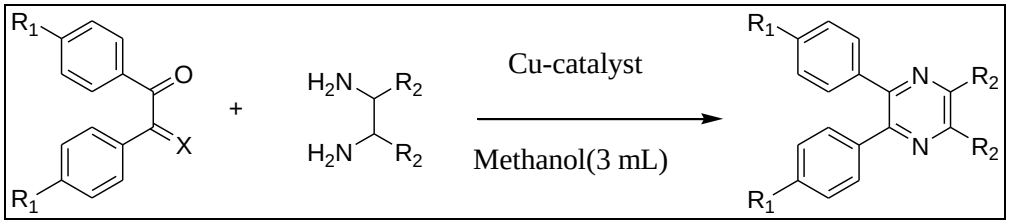
6	5	Acetonitrile	-	16	< 30
7	-	Dichloromethane	-	16	< 25
8	-	Chloroform	-	16	Trace amount
9[f]	-	Water	-	12	<40
10[g]		Methanol	-	12	>10
11[g]		-	Reflux	8	52 [h]
12[i]	**5**	**-**	**50**	**3**	**92**
13	5	-	Reflux	3	-
14	2.5	-	50	4	72
15	-	-	Reflux	4	75
16	1.5	-	Reflux	6	69
17	1	-	Reflux	8	64
18	0.5	-	Reflux	6	60

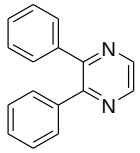
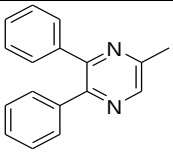
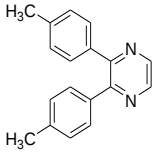
[a]reaction of benzil (1 mmol), ethane-1,2-di amine (1 mmol), 3mL solvent and Cu-catalyst was taken for every reaction; [b] yield was isolated yield after column chromatography; [c] primary effort for synthesis of pyrazine; [d]both pyrazine and dihydro pyrazine was observed; [e] no dihydro pyrazine was identified; [f] we used surfactant during reaction; [g] reaction was done without catalyst; [h] no development in yield after 8 h; [I] optimized reaction condition.

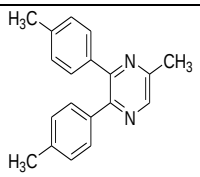
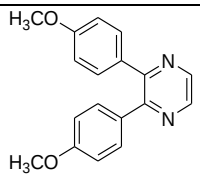
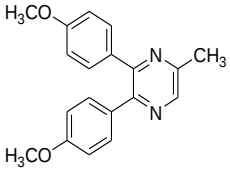
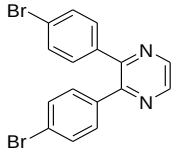
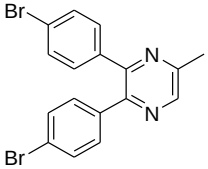
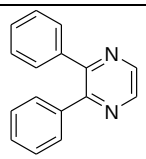
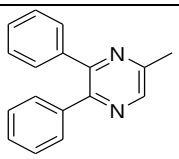
To search the generality of our process, some structurally as well as chemically diversified 1, 2-diketones and 1,2-diamines are used for the reaction, at optimized condition and find striking result in each instance (table. IV. B. 2). Moreover, the catalyst also helps to proceeds a tandem

oxidation-cyclisation of *α*-hydroxy ketone during the reaction with alkyl *vic*-diamine or 2-methyl substituted alkyl *vic*-diamine to their respective pyrazine or methylated pyrazines (entry 9 and 10 of table. IV. B. 2). The equal efficiency of the catalyst for both substituted (electron donating or electron withdrawing)/unsubstituted benzil and also for *α*-hydroxy ketone, initiate us to consider the effect of catalyst on other predecessor for the double condensation-cyclization reactions to prepared respective pyrazines. To check, we switch one or both aromatic rings of *vic*-diketones with aliphatic ones and do reaction at our optimized condition with varying *vic*-diamines (table. IV. B. 3). Again, we find sustaining results for the preparation of the corresponding pyrazines. Further, we observed similar effectivity of the catalyst during condensation reaction of 2, 3-diaminomaleonitrile with *vic*-diketone/*α*-hydroxy ketone (table. IV. B. 4) for cyano-pyrazine preparation.

Table IV. B. 2: Synthesis of pyrazine analogue by optimized reaction condition [a]:

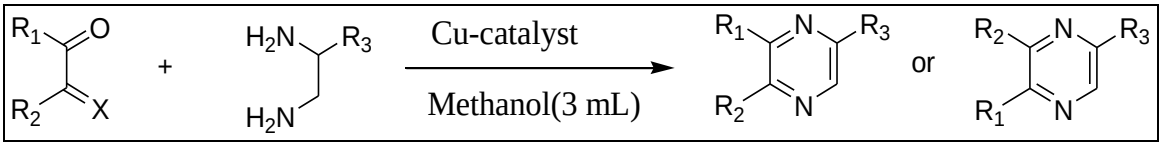


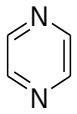
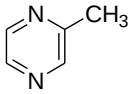
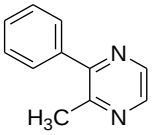
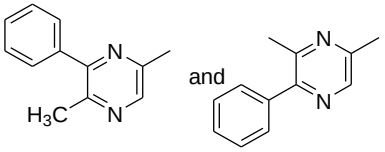
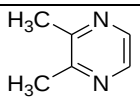
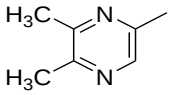
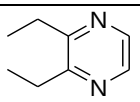
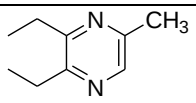
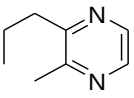
Entry	R_1	R_2	X	Time (h)	Product	Yield [b] (%)
1	-H	-H	O	3		92
2	-	$-CH_3$	-	3		91
3	$-CH_3$	-H	-	$3^{1/2}$		90

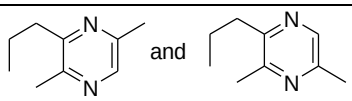
4	-	$-CH_3$	-	-		91
5	$-OCH_3$	-H	-	4		86
6	-	$-CH_3$	-	4		89
7	-Br	-H	-	$4^{1/2}$		85
8	-Br	$-CH_3$	O	$3^{1/2}$		80
9	-H	-H	-OH	3		91
10	-	$-CH_3$	-	3		92

[a] diketone/α-hydroxy ketone (1 mmol), diamine (1 mmol), catalyst (5 mol%), methanol (3 ml) at 50^0 C. [b] all yields are isolated yields.

Table IV. B. 3: Screening the effectiveness of catalyst for pyrazine analogue at optimized reaction condition [a]:

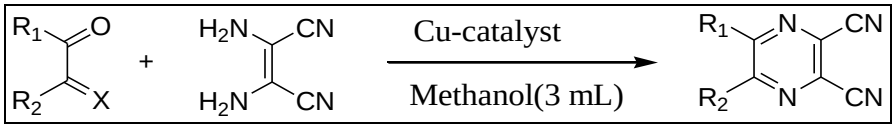


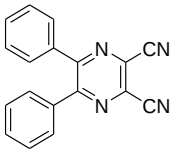
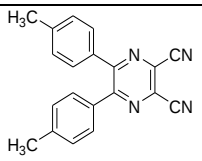
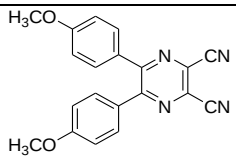
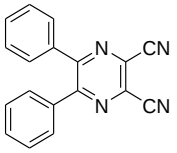
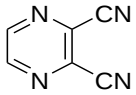
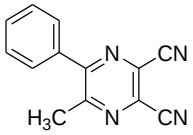
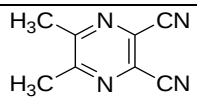
Entry	R_1	R_2	R_3	X	Time (h)	Product	Yield [b](%)
1[c]	-H	-H	-H	O	3		90
2[c]	-H	-H	$-CH_3$	-	3		92
3	-Ph	$-CH_3$	-H	-	4		89
4	-	-	$-CH_3$	-	$4^{1/2}$		Mixture
5	$-CH_3$	$-CH_3$	-H	-			85
6	$-CH_3$	$-CH_3$	$-CH_3$	-			
7	$-C_2H_5$	$-C_2H_5$	-H	-	$3^{1/2}$		89
8	-	-	$-CH_3$	-	-		90
9	$-C_3H_7$	$-CH_3$	-H	-	4		84

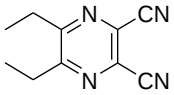
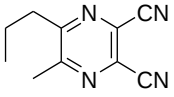
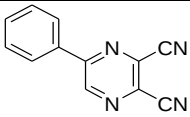
10	-	-	-H	-	-		Mixture

[a] diketone/α-hydroxy ketone (1 mmol), diamine (1 mmol), catalyst (5 mol%), methanol (3 ml) at 50^0 C. [b] all yields are isolated yields. [c] reaction was done in room temperature.

Table IV. B. 4: Preparation of cyano-pyrazine at our optimized reaction condition [a]:

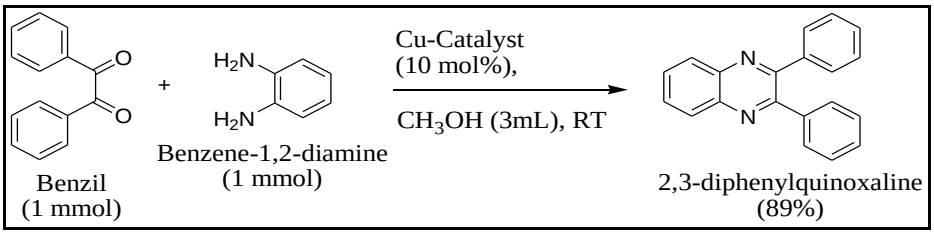


Entry	R_1	R_2	X	Time (h)	Product	Yield[b] (%)
1	$-C_6H_5$	$-C_6H_5$	O	4		91
2	p-Me-C_6H_5-	p-Me-C_6H_5-	-	$4^{1/2}$		90
3	p-OCH_3-C_6H_5-	p-OCH_3-C_6H_5-	-	4		85
4	$-C_6H_5$	$-C_6H_5$	-OH	$4^{1/2}$		89
5[c]	-H	-H	O	3		78
6	$-C_6H_5$	$-CH_3$	O	$3^{1/2}$		89
7	$-CH_3$	$-CH_3$	O	3		90

8	$-C_2H_5$	$-C_2H_5$	O	4		79
9	$-C_3H_7$	$-CH_3$	O	4		84
10	$-C_6H_5$	-H	O	$4^{1/2}$		82

[a] diketone/α-hydroxy ketone (1 mmol), 2, 3-diaminomaleonitrile (1 mmol), catalyst (5 mol%), methanol (3 ml) at 50^0 C. [b] all yields are isolated yields. [c] reaction was done at room temperature.

Successful catalytic role during the double condensation/tandem oxidation-cyclisation process for the preparation of pyrazines encourages us to expand the synthetic scope of our catalyst. Hence, we used o- phenylene diamine (1 mmol) and benzil (1 mmol) in presence of copper catalyst (10 mol %) in methanol (3 mL) to prepare 2,3-diphenyl quinoxaline at room temperature (scheme. IV. B. 2). Again, we were able to achieve an optimized reaction condition (entry 10 of table. IV. B. 5), which also serves well for other substituted *vic*-diketone/α-hydroxy ketone to furnish their corresponding quinoxalines in moderate to good yield (table. IV. B. 6).



Scheme. IV. B. 2. Quinoxaline preparation via condensation cyclisation process

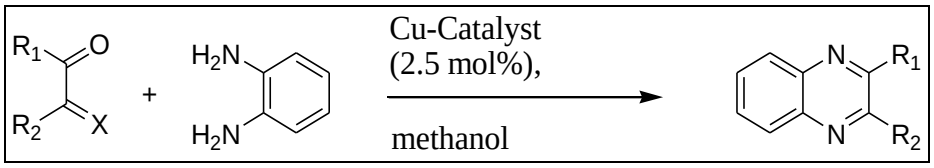
Table IV. B. 5: Optimization of reaction condition for the preparation of 2,3-diphenyl quinoxaline:

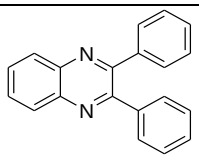
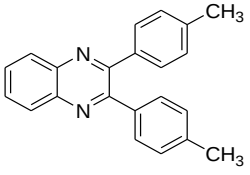
Entry	Solvent (3 mL)	Catalyst (mol %)	Temp (^{0} C)	Time (h)	Yield[a] (%)
1	Methanol	10	Room temp	1	-
2	-	-	-	3	45

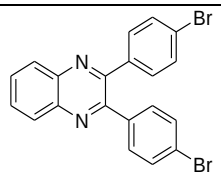
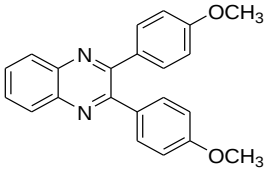
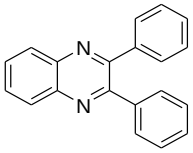
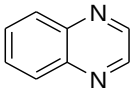
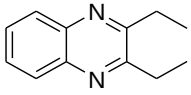
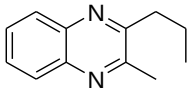
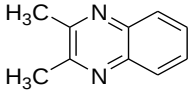
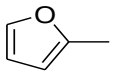
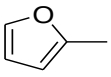
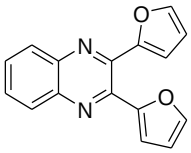
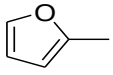
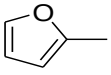
3	-	-	-	6	65
4[b]	-	-	-	9	89
5	Acetonitrile		-	16	35
6	Dichloromethane		-	16	46
7	Chloroform		-	16	38
8	Water		-	12	20
9	Methanol	5	-	12	89
10[c, d]	-	**2.5**	**40**	**3**	**90**
11	-	1.5	reflux	6	85
12	-	0.5	Reflux	6	72

[a] yield are isolated yields, [b] yield of product remains unchanged after 12h, [c] product yield remains unchanged after 6h, [d] optimized reaction condition: benzil (1 mmol), o- phenylene diamine (1 mmol) copper catalyst (2.5 mol%) and methanol (3 mL).

Table no. IV. B. 6: Generality of optimized conditionfor 2, 3-disubstituted quinoxaline [a]:



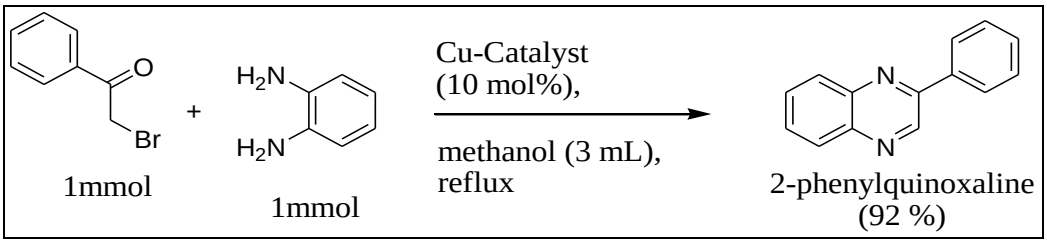
Entry	R1	R2	X	Time (h)	Product	Yield [b] (%)
1	-C_6H_5	-C_6H_5	O	3		90
2	pCH_3-C_6H_5-	pCH_3-C_6H_5-	-	3		87

3	pBr-C_6H_5-	pBr-C_6H_5-	-	$3^{1/2}$		89
4	pCH_3O-C_6H_5-	pCH_3O-C_6H_5-	-	4		85
5	-C_6H_5	-C_6H_5	-OH	$3^{1/2}$		90
6	-H	-H	O	3		89
7	-C_2H_5	-C_2H_5	O	4		91
8	-C_3H_7	-CH_3	O	$3^{1/2}$		82
9.	-CH_3	-CH_3	O	3		84
10.			O	4		86
11.			-OH	$4^{1/2}$	-	83

[a]1, 2-di ketone (1 mmol), o- phenylene diamine (1 mmol), Cu (II)-catalyst (2.5 mol %) and methanol (3 mL) at 40 ^{0} C, [b] yields are isolated yields.

Further, we scrutinized capability of the catalyst against other most useful synthetic protocol for quinoxaline preparation, i.e., reaction of phenacyl bromide/substituted phenacyl bromide and *vic*-diamine. For the initial measure we choose phenacyl bromide (1 mmol), o- phenylene diamine (1

mmol), copper catalyst (10 mol %) and Na_2CO_3 (1 equiv.) in methanol (3 mL) under reflux condition. We get satisfactory yield of the expected quinoxaline product, i.e., 2-Phenyl quinoxaline (92 %) (scheme IV. B. 3). On further investigating of our reaction we find the initial reaction condition (i.e., phenacyl bromide (1 mmol), o- phenylene diamine (1 mmol), copper catalyst (10 mol %) and Na_2CO_3 (1 equiv.) in methanol (3 mL) under reflux condition) as our optimized reaction condition (entry. 1 of table. IV. B. 7). Further, the applicability towards other substituted phenacyl bromide or *vic*-diamine proves the effectiveness and generality of our optimized reaction condition (table. IV. B. 8).



Scheme IV. B. 3. Preparation of 2-phenylquinoxaline

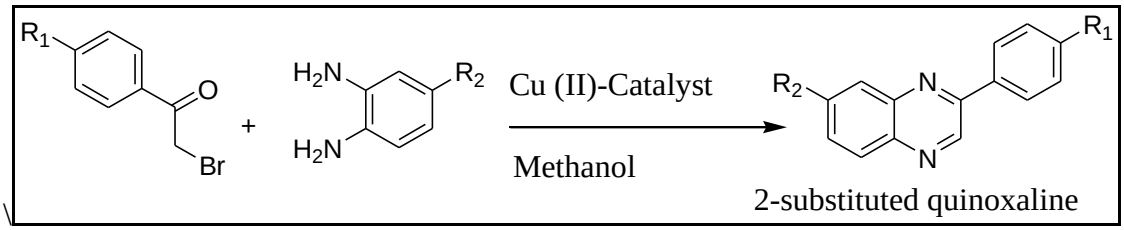
Table IV. B. 7: Scrutiny of optimized reaction condition for preparation of 2-phenyl quinoxaline:

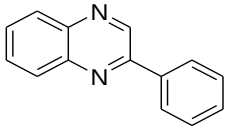
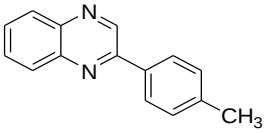
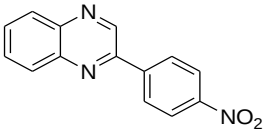
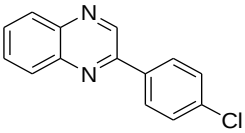
Entry	Solvent (3 mL)	Catalyst (mol %)	Base[a]	Temp (^{0} C)	Time (h)	Yield[b] (%)
1[c, d]	**Methanol**	**10**	**Na_2CO_3**	**reflux**	**3**	**92**
2	-	-	-	-	6	-
3[e]	-	-	-	50	6	75
4	-	5	-	reflux	12	42
5	Acetonitrile	10	-	-	16	50
6	Dichloromethane	-	-	-	16	42

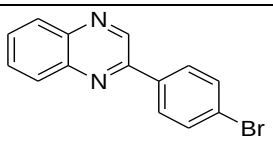
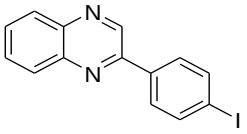
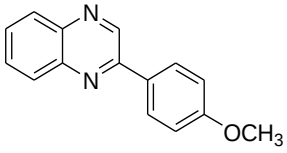
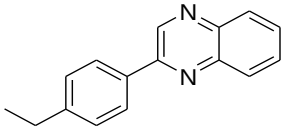
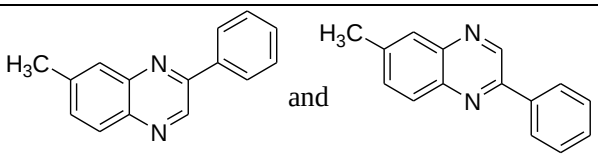
7	Chloroform	-	-	-	16	29
8	Water	-	-	-	12	Nr

[a] base was taken in 1 equivalent, [b] yields are isolated yields, c reaction was also checked using bases like KOH, $NaHCO_3$ and K_2CO_3 in 1 equiv. amount but the yield was not satisfactory, [d] our optimized reaction condition (i.e. phenacyl bromide (1 mmol), o- phenylene diamine (1 mmol), copper catalyst (10 mol%), Na_2CO_3 (1 equiv.) and methanol (3 mL), [e] no change of yield was observed upto 12 h.

Table IV. B. 8: Generality of the optimized reaction condition for preparation of 2-substituted quinoxaline [a]:



Entry	R_1	R_2	Time (h)	Product	Yield (%)
1	-H	-H	3		92
2	$-CH_3$	-H	3		90
3	$-NO_2$	-	$3^{1/2}$		85
4	-Cl	-	4		83

5	-Br	-	4		86
6	-I	-	4		85
7	-OCH_3	-	$3^{1/2}$		90
8.	-C_2H_5	-	3		82
9.	-H	-CH_3	$3^{1/2}$	 and	Mixture of product was obtained

[a] optimized reaction condition (i.e. substituted phenacyl bromide (1 mmol), substituted o-phenylene diamine (1 mmol), copper catalyst (10 mol%), Na_2CO_3 (1 equiv.) and methanol (3 mL)

IV. B. 2. Experimental:

Scanning electron micrograph of the synthesized copper (II) complex have been analyzed using Inspect F-50 FEI scanning electron microscope with SEM accelerating voltage of 10.00 kV and magnification of 20000X. ^{1}H NMR and ^{13}C NMR were recorded on Bruker Advance FT-NMR (300 MHz) Spectrometer using TMS as internal standard.

IV. B. 2. 1. Reaction procedure:

IV. B. 2. 1. 1. General procedure for the preparation of Cu II-Catalyst:

A mixture of 3, 5-dinitrobenzoic acid (0.1688 g), $Cu(NO_3)_2.3H_2O$ (0.1932 g) and melamine (0.1002 g) was taken and grind to dust in a mortar pistol. To the mixture 1.5 mL of distilled water was added and stirred for 30m until we get a suspension. Then the reaction mixture was sealed in a 10 mL Teflon-lined stainless-steel autoclave and heated for 45 h at 423 K. After that

the autoclave was subjected to cooling (for 5 h) to room temperature. The reaction mixture was filtered and was subsequently wash with distilled water. We get blue colored crystal of the product, which we take for further characterization by single crystal X-ray diffraction and SEM.

IV. B. 2. 1. 2. General Process for the preparation of substituted pyrazine:

A mixture of substituted *vic*-diketone/α-hydroxy ketone (1 mmol), substituted ethane-1,2-diamine (1 mmol), catalyst (5 mol %) and methanol (3 mL) was taken in a50mL round bottom flask and heated in an oil bath at 50^0C with proper stirring on magnetic stirrer for specified time (table. IV. B. 2 and 3). The progress of reaction was monitored by TLC. After the completion of the reaction the product was extracted with Ethyl acetate and further purified by Column Chromatography using silica gel 60-120 mesh. Solid product obtained from column chromatography was recrystallized using ethyl acetate and pet ether.

IV. B. 2. 1. 3. General Process for the preparation of substituted cyano-pyrazine:

A mixture of substituted diketone/α-hydroxy ketone (1 mmol), 2, 3-diaminomaleonitrile (1 mmol), catalyst (5 mol%) and methanol (3 mL) was taken in a50mL round bottom flask and heated in an oil bath at 50^0C with proper stirring on magnetic stirrer for specified time (table. IV. B. 4). The progress of reaction was monitored by TLC. After the completion of the reaction the product was extracted with Ethyl acetate and further purified by Column Chromatography using silica gel 60-120 mesh. Solid product obtained from column chromatography was recrystallized using ethyl acetate and pet ether.

IV. B. 2. 1. 4. General Process for the preparation of 2, 3-disubstituted quinoxaline:

A mixture of substituted benzil (1 mmol), o- phenylene diamine (1 mmol), copper catalyst (2.5 mol%) and methanol (3 mL) was taken in a50 mL round bottom flask and heated in an oil bath at 40^0 C with proper stirring on magnetic stirrer for specified time (table. IV. B. 6). The progress of reaction was monitored by TLC. After the completion of the reaction the product was extracted with Ethyl acetate and further purified by Column Chromatography using silica gel 60-120 mesh.

IV. B. 2. 1. 5. General Process for the preparation of 2-substitutedquinoxaline:

A mixture of phenacyl bromide (1 mmol), o- phenylene diamine (1 mmol), copper catalyst (10 mol %), Na_2CO_3 (1 equiv.) and methanol (3 mL) was taken in a 50mL round bottom flask and refluxed for specified time (table. IV. B. 8). The progress of reaction was monitored by TLC.

After the completion of the reaction the product was extracted with Ethyl acetate and further purified by Column Chromatography using silica gel 60-120 mesh.

IV. B. 2. 2. Chemicals:

All the chemicals used in this investigation including their purity and sources are summarized in the following table (table. IV. B. 9).

Table IV. B. 9: Chemicals used for present investigation:

Entry	Chemical	Sources	Purity (%)
1	Ethylene diamine	SRL	99.5
2	1, 2-diamino propane	Sigma-Aldrich	99
3	4, 4’-Dimethyl benzil	Sigma-Aldrich	97
4	4,4’-Dimethoxybenzil	Sigma-Aldrich	98
5	4,4’-Dibromo benzil	Sigma-Aldrich	90
6	Glyoxal	SRL	-
7	2,3-Hexadione	Sigma-Aldrich	90
8	3,4-Hexadione	Sigma-Aldrich	95
9	Diacetyl	S.D. Fine	-
10	Diamino malononitrile	Sigma-Aldrich	98
11	o-phenylene diamine	SR	99
12	Furil	Sigma-Aldrich	98
13	Furoin	Sigma-Aldrich	98
14	2-bromo acetophenone	Sigma-Aldrich	99
15	2-bromo-4’-nitro acetophenone	Sigma-Aldrich	95
16	2-bromo-4’-chloro acetophenone	Sigma-Aldrich	98

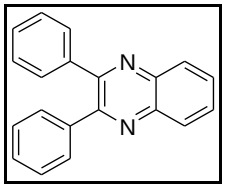
17	2, 4'-dibromo acetophenone	Sigma-Aldrich	98
18	2-bromo-4'- methyl acetophenone	Sigma-Aldrich	90
19	2-bromo-4'- methoxyacetophenone	Sigma-Aldrich	97
20	$CDCl_3$for NMR	S.D. Fine	97
21	Petroleum ether	Thomas Baker	98
22	Ethyl acetate	Thomas Baker	99
23	Silica-gel 60-120 mesh for column	SRL	-
24	Silica-gel for TLC	SRL	-
25	Na_2SO_4anhydrous	SRL	99.5
26	Benzil	SRL	98
27	3,5-Dinitrobenzoic acid	Sigma-Aldrich	99
28	Cu $(NO_3)_2.3H_2O$	SRL	99.5
29	Melamine	Sigma-Aldrich	99

IV. B. 3. Conclusion:

From the above findings it can be concluded that a milder and greener reaction protocols for preparation of both quinoxaline and pyrazine derivatives have been developed. The application of polymeric copper (II) catalyst has also been established.

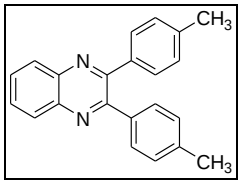
IV. B. 4. Spectral data:

IV. B. 4. 1. 2, 3-Diphenylquinoxaline:



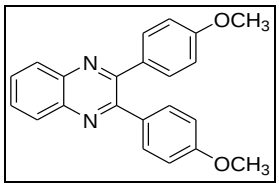
^{1}H NMR ($CDCl_3$, 300MHz): 7.25-7.33 (m, 6H), 7.50-7.65 (m, 6H), 8.11-8.14 (m, 2H); ^{13}C NMR ($CDCl_3$, 75MHz):128.1, 128.6, 129.0, 129.8, 138.9, 141.0, 153.2 ppm.

IV. B. 4. 2. 2, 3-Di-*p*-tolylquinoxaline:



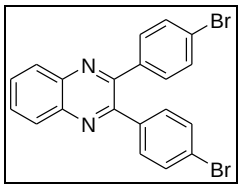
^{1}H NMR ($CDCl_3$, 300MHz): 2.32 (s, 6H), 7.10 (d, 4H, *J* = 8.1 Hz), 7.43 (d, 4H, *J* = 7.8 Hz), 7.65-7.68 (dd, 2H, *J* = 3.3 and 6.3 Hz), 8.11-8.14 (dd, 2H, *J* = 3.3 and 6.3 Hz); ^{13}C NMR ($CDCl_3$, 75MHz): 21.3, 128.9, 129.0, 129.6, 129.7, 136.3, 138.6, 141.1 ppm.

IV. B. 4. 3. 2, 3-Bis (4-methoxyphenyl) quinoxaline:



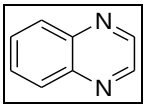
^{1}H NMR ($CDCl_3$, 300MHz): 3.83 (s, 6H), 6.87 (d, 4H, *J* = 8.4 Hz), 7.49 (d, 4H, *J* = 8.7 Hz), 7.70-7.73 (dd, 2H, *J* = 3.6 and 6.3 Hz), 8.11-8.14 (dd, 2H, *J* = 3.6 and 6.3 Hz); ^{13}C NMR ($CDCl_3$, 75MHz): 55.3, 113.8, 129.0, 129.6, 131.3, 131.8, 141.1, 153.0, 160.2 ppm.

IV. B. 4. 4. 2, 3-Bis (4-bromophenyl) quinoxaline:



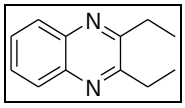
^{1}H NMR ($CDCl_3$, 300MHz): 7.38 (d, 4H, *J* = 8.1 Hz), 7.48 (d, 4H, *J* = 8.4 Hz), 7.78-7.75 (dd, 2H, *J* = 6.3 and 3.3 Hz), 8.12-8.15 (dd, 2H, *J* = 6.3 and 3.3 Hz); ^{13}C NMR ($CDCl_3$, 75MHz): 123.7, 129.1, 130.4, 131.4, 131.6, 137.6, 141.1, 151.8 ppm.

IV. B. 4. 5. Quinoxaline:



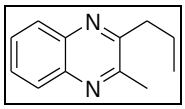
^{1}H NMR ($CDCl_3$, 300MHz): 7.70 (m, 2H), 8.07-8.11 (m, 2H), 8.81-8.84 (m, 2H); ^{13}C NMR ($CDCl_3$, 75MHz): 129.4, 130.0, 142.9, 144.9 ppm.

IV. B. 4. 6. 2, 3-Diethylquinoxaline:



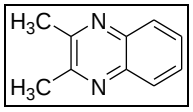
^{1}H NMR ($CDCl_3$, 300MHz): 1.43 (t, 6H, *J* = 7.5 Hz), 3.01-3.08 (q, 4H, *J* = 7.5 Hz), 7.63-7.66 (dd, 2H, *J* = 3.3 and 6.3 Hz), 8.00-8.04 (dd, 2H, *J* = 3.3 and 6.3 Hz); ^{13}C NMR ($CDCl_3$, 75MHz): 12.5, 28.3, 128.6, 141.0, 157.2 ppm.

IV. B. 4. 7. 2-Methyl-3-propylquinoxaline:



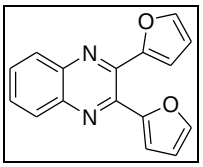
^{1}H NMR ($CDCl_3$, 300MHz): 1.09 (t, 3H, *J* = 7.2 Hz), 1.81-1.91 (sextet, 2H, *J* = 7.5 Hz), 2.77 (s, 3H), 2.95-3.00 (t, 2H, *J* = 7.5 Hz), 7.64-7.68 (m, 2H), 7.97-8.03 (m, 2H); ^{13}C NMR ($CDCl_3$, 75MHz): 14.2, 21.5, 22.8, 37.8, 128.2, 128.5, 128.8, 128.9, 140.8, 141.1, 153.2, 156.7 ppm.

IV. B. 4. 8. 2, 3-Dimethylquinoxaline:



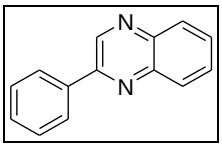
^{1}H NMR ($CDCl_3$, 300MHz): 2.71 (s, 6H), 7.63-7.66 (dd, 2H, *J* = 3.3, 6.3 Hz), 7.95-7.99 (dd, 2H, *J* =3.3, 6.3 Hz); ^{13}C NMR ($CDCl_3$, 75MHz): 23.1, 128.3, 128.8, 141.0, 153.4 ppm.

IV. B. 4. 9. 2, 3-Di (furan-2-yl)-quinoxaline:



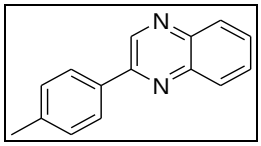
^{1}H NMR ($CDCl_3$, 300MHz): 2.56 (s, 3H), 6.55-6.70 (m, 4H), 7.47-7.62 (m, 3H), 7.92-8.04 (m, 2H); ^{13}C NMR ($CDCl_3$, 75MHz): 21.8, 111.8, 112.5, 127.9, 128.5, 132.7, 139.0, 140.6, 140.9, 141.7, 142.5, 143.9, 144.0, 150.9 ppm.

IV. B. 4. 10. 2-Phenyl quinoxaline:



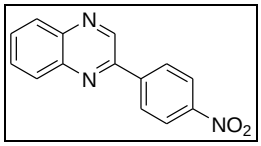
^{1}H NMR ($CDCl_3$, 300 MHz): 6.91-6.96 (m, 3H), 7.08-7.17 (m, 2H), 7.48-7.58 (m, 4H), 8.75 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): 127.5, 129.1, 129.5, 129.6, 130.1, 136.7, 141.5, 142.2, 143.3, 151.8 ppm.

IV. B. 4. 11. 2-*p*-Tolylquinoxaline:



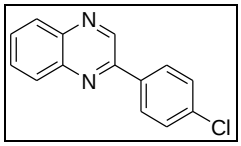
^{1}H NMR ($CDCl_3$, 300 MHz): 2.43 (s, 2H), 7.35 (d, 2H, J = 7.8 Hz), 7.71-7.77 (m, 2H), 8.08-8.15 (m, 4H), 9.31 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): 21.43, 126.0, 127.4, 128.9, 129.3, 129.5, 129.9, 130.5, 131.3, 133.8, 140.2, 140.5, 141.2, 143.1, 151.84 ppm.

IV. B. 4. 12. 2-(3-Nitrophenyl) quinoxaline:



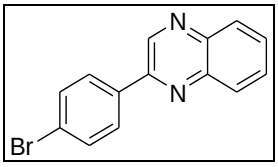
^{1}H NMR ($CDCl_3$, 300 MHz): 7.76-7.86 (m, 3H), 8.15-8.21 (m, 2H), 8.38 (d, 1H, J = 6.3 Hz), 8.55 (d, 1H, J = 7.5 Hz), 9.11 (s, 1H), 9.39 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): 122.5, 124.7, 129.2, 129.8, 130.2, 130.6, 130.9, 133.0, 138.4, 142.0, 142.2, 149.0, 149.1 ppm

IV. B. 4. 13. 2-(4-Chlorophenyl) quinoxaline:



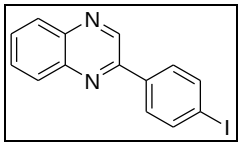
^{1}H NMR ($CDCl_3$, 300 MHz): 7.54 (d, 2H, J = 8.4 Hz), 7.78-7.94 (m, 2H), 8.15 (d, 4H, J = 8.4 Hz), 9.32 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): 128.8, 129.0, 129.4, 129.6, 130.6, 135.1, 136.7, 141.4, 142.3, 142.7, 150.7 ppm.

IV. B. 4. 14. 2-(4-Bromophenyl) quinoxaline:



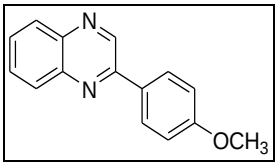
^{1}H NMR ($CDCl_3$, 300 MHz): 7.68-7.71 (m, 2H), 7.75-7.78 (m, 2H), 8.07-8.16 (m, 4H), 9.29 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): 125.0, 129.0, 129.6, 129.9, 130.5, 132.3, 135.6, 141.6, 142.2, 142.7, 150.6 ppm.

IV. B. 4. 15. 2-(4-Iodophenyl) quinoxaline:



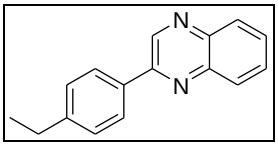
^{1}H NMR ($CDCl_3$, 300 MHz): 7.30- 7.68 (m, 4H), 8.01-8.11 (m, 4H), 9.27 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): 99.0, 125.8, 128.9, 129.3, 129.5, 130.7, 135.2, 136.5, 141.4, 142.4, 142.5, 150.3 ppm.

IV. B. 4. 16. 2-(4-Methoxyphenyl) quinoxaline:



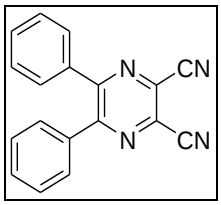
^{1}H NMR ($CDCl_3$, 300 MHz): 3.89 (s, 3H), 7.08 (s, 2H), 7.70-7.76 (m, 2H), 8.08-8.18 (m, 4H), 9.29 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): 55.5, 114.6, 129.00, 129.05, 129.2, 130.3, 141.1, 142.2, 143.1, 151.4, 161.5 ppm.

IV. B. 4. 17. 2-(4-Ethylphenyl) quinoxaline:



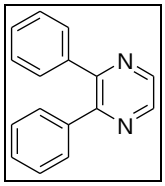
^{1}H NMR ($CDCl_3$, 300 MHz):1.26-1.33 (m, 3H), 2.74 (q, 2H, J = 7.5 Hz), 7.35 (d, 2H, J = 8.1 Hz), 7.74 (q, 2H J = 7.5 Hz), 8.09-8.15 (m, 4H), 9.30 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): 15.4, 28.8, 127.5, 128.7, 129.0, 129.3, 129.5, 130.2, 134.1, 141.3, 142.3, 143.2, 146.8, 151.8 ppm.

IV. B. 4. 18. 5, 6-Diphenylpyrazine-2,3-dicarbonitrile:



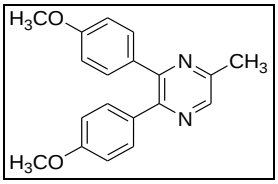
^{1}H NMR ($CDCl_3$, 300 MHz): 7.34-7.62 (m, 10H); ^{13}C NMR ($CDCl_3$, 75 MHz): 112.4, 128.2, 129.2, 130.5, 133.3, 134.5, 154.6 ppm.

IV. B. 4. 19. 2, 3-diphenylpyrazine:



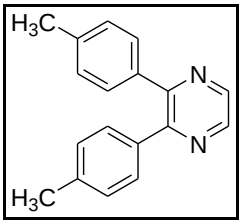
^{1}H NMR ($CDCl_3$, 300 MHz): 6.38-6.59 (m, 10H), 7.73(s, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): 128.3, 128.7, 129.6, 138.6, 142.1, 152.9 ppm.

IV. B. 4. 20. 2, 3-bis(4-methoxyphenyl)-5-methylpyrazine:



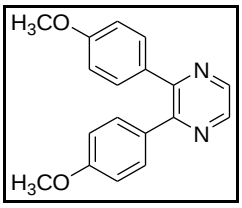
^{1}H NMR ($CDCl_3$, 300 MHz): 2.59 (s, 3H), 3.74 (s, 6H), 6.75 (d, 4H, J=8.7Hz), 7.35 (d, 4H, J=8.7 Hz), 8.36 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): 23.0, 53.5, 55.2, 113.4, 129.6, 130.6, 151.1, 150.1, 158.6, 159.6 ppm.

IV. B. 4. 21. 2,3-di*p*-tolylpyrazine:



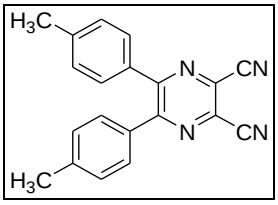
^{1}H NMR ($CDCl_3$, 300 MHz): 2.34 (s, 6H), 7.05-7.46 (m, 8H), 8.52 (s, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): 21.3, 129.0, 129.5, 135.9, 138.6, 141.7, 152.6 ppm.

IV. B. 4. 22. 2, 3-bis (4-methoxyphenyl) pyrazine:



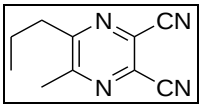
^{1}H NMR ($CDCl_3$, 300 MHz): 3.77 (s, 6H), 6.75-7.43 (m, 8H), 8.46 (s, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): 55.2, 113.7, 130.9, 131.2, 141.5, 152.1, 159.9 ppm.

IV. B. 4. 23. 5, 6-di*p*-tolylpyrazine-2, 3-dicarbonitrile:



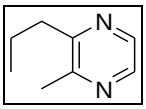
^{1}H NMR ($CDCl_3$, 300 MHz): 2.28-2.42 (m, 6H), 6.97-8.01 (m, 8H); ^{13}C NMR ($CDCl_3$, 75 MHz): 21.2, 21.6, 118.8, 126.8, 128.6, 128.9, 129.1, 129.3, 129.8, 130.0, 131.1, 132.2, 139.2, 144.0, 144.3, 156.8 ppm.

IV. B. 4. 24. 5-methyl-6-propylpyrazine-2,3-dicarbonitrile:



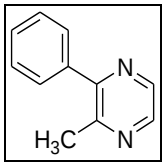
^{1}H NMR ($CDCl_3$, 300 MHz): 1.06 (t, 3H, J= 7.2 Hz), 1.78-1.88 (m, 2H), 2.75 (s, 3H), 2.94 (t, 2H, J= 7.8 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): 13.8, 20.4, 22.2, 36.9, 113.3, 129.9, 130.4, 157.8, 161.2 ppm.

IV. B. 4. 25. 2-Methyl-3-propylpyrazine:



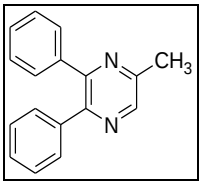
^{1}H NMR ($CDCl_3$, 300 MHz): 0.90-1.04 (m, 3H), 1.70-1.82 (m, 2H), 2.58 (s, 3H), 2.79 (t, 2H, J= 7.5 Hz), 8.28 (s, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): 14.1, 21.5, 21.7, 141.2, 141.4, 152.3, 156.1 ppm.

IV. B. 4. 26. 2-Methyl-3-phenylpyrazine:



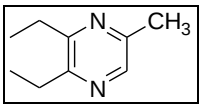
^{1}H NMR ($CDCl_3$, 300 MHz): 2.54 (s, 3H), 7.42-7.60 (m, 5H), 8.44 (d, 2H, J= 2.4); ^{13}C NMR ($CDCl_3$, 75 MHz): 23.2, 128.4, 128.8, 128.9, 138.6, 141.6, 142.2, 151.8, 154.0 ppm.

IV. B. 4. 27. 5-Methyl-2,3-diphenylpyrazine:



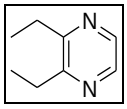
^{1}H NMR ($CDCl_3$, 300 MHz): 1.86 (s, 3H), 6.48-6.64 (m, 10H), 7.68 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): 20.5, 127.4, 127.6, 128.8, 137.9, 141.1, 148.8, 150.3, 150.7 ppm.

IV. B. 4. 28. 2, 3-Diethyl-5-methylpyrazine:



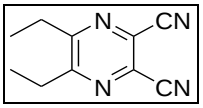
^{1}H NMR ($CDCl_3$, 300 MHz): 1.26-1.31 (m, 6H), 2.53 (s, 3H), 2.82 (q, 4H, J= 7.5), 8.2 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): 13.1, 13.4, 21.0, 27.1, 27.6, 140.8, 149.9, 152.9, 155.3 ppm.

IV. B. 4. 29. 2,3-Diethylpyrazine:



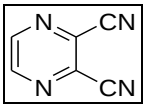
^{1}H NMR ($CDCl_3$, 300 MHz): 1.32 (t, 6H, J= 7.5 Hz), 2.86 (q, 4H, J= 7.5 Hz), 8.33 (s, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): 12.8, 27.6, 141.3, 156.6 ppm.

IV. B. 4. 30. 5,5-Diethylpyrazine-2,3-dicarbonitrile:



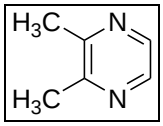
^{1}H NMR ($CDCl_3$, 300 MHz): 1.39- 1.44 (m, 6H), 2.62 (q, 4H, J= 7.5 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): 13.8, 29.1, 113.4, 130.4, 158.0 ppm.

IV. B. 4. 31. Pyrazine-2,3-dicarbonitrile:



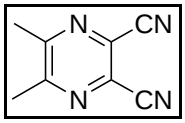
^{1}H NMR ($CDCl_3$, 300 MHz): 8.90 (s, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): 114.3, 135.0, 151.0 ppm.

IV. B. 4. 32. 2, 3-Dimethyl pyrazine:



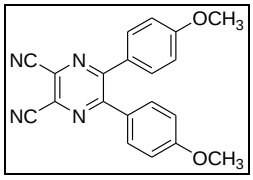
^{1}H NMR ($CDCl_3$, 300 MHz): 2.54 (s, 6 H), 8.45 (s, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): 23.1, 141.6, 142.1, 151.8 ppm.

IV. B. 4. 33. 5, 6-dimethylpyrazine-2,3-dicarbonitrile:



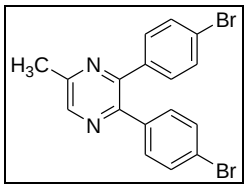
^{1}H NMR ($CDCl_3$, 300 MHz): 2.54 (s, 6 H); ^{13}C NMR ($CDCl_3$, 75 MHz): 23.2, 114.1, 141.9, 150.0 ppm.

IV. B. 4. 34. 5, 6- bis-(4-methoxyphenyl) pyrazine-2,3-dicarbonitrile:



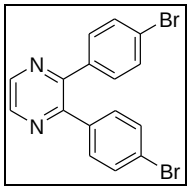
^{1}H NMR ($CDCl_3$, 300 MHz): 3.77 (s, 6 H), 6.75-7.43 (m, 8H); ^{13}C NMR ($CDCl_3$, 75 MHz): 55.2, 113.7, 113.8, 130.9, 131.2, 141.5, 152.1, 159.9 ppm.

IV. B. 4. 35. 2, 3-bis-(4-bromophenyl)-5-methylpyrazine:



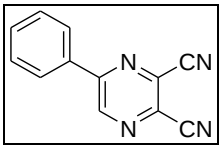
^{1}H NMR ($CDCl_3$, 300 MHz): 2.16 (s, 3 H), 7.16-7.50 (m, 8H) 8.45(s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): 20.5, 127.4, 127.6, 128.7, 128.8, 137.9, 141.1, 148.9, 150.3, 150.7 ppm.

IV. B. 4. 36. 2, 3-bis-(4-bromophenyl)-pyrazine:



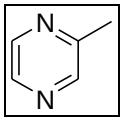
^{1}H NMR ($CDCl_3$, 300 MHz): 7.16-7.49 (m, 8H) 8.71(s, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): 127.4, 127.6, 128.7, 128.8, 137.9, 141.1, 148.9, 150.3, 157.7 ppm.

IV. B. 4. 37. 5-phenylpyrazine-2, 3-dicarbonitrile:



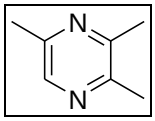
^{1}H NMR ($CDCl_3$, 300 MHz): 7.60-8.15 (m, 5H), 9.30 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): 112.9, 113.1, 128.0, 129.8, 130.8, 132.5, 133.0, 133.3, 144.1, 154.9 ppm.

IV. B. 4. 38. 2-methylpyrazine:



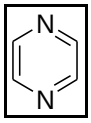
^{1}H NMR ($CDCl_3$, 300 MHz): 2.54 (s, 3H), 8.41-8.51 (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): 21.0, 140.9, 142.0, 145.0, 153.6 ppm.

IV. B. 4. 39. 2, 3, 5-trimethylpyrazine:



^{1}H NMR ($CDCl_3$, 300 MHz): 2.14 (s, 9H), 8.13 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): 21.1, 140.9, 142.1, 145.0, 153.6 ppm.

IV. B. 4. 40. Pyrazine:



^{1}H NMR ($CDCl_3$, 300 MHz): 8.7 (s, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz): 148.9 ppm.

IV. B. 5: Supporting spectra:

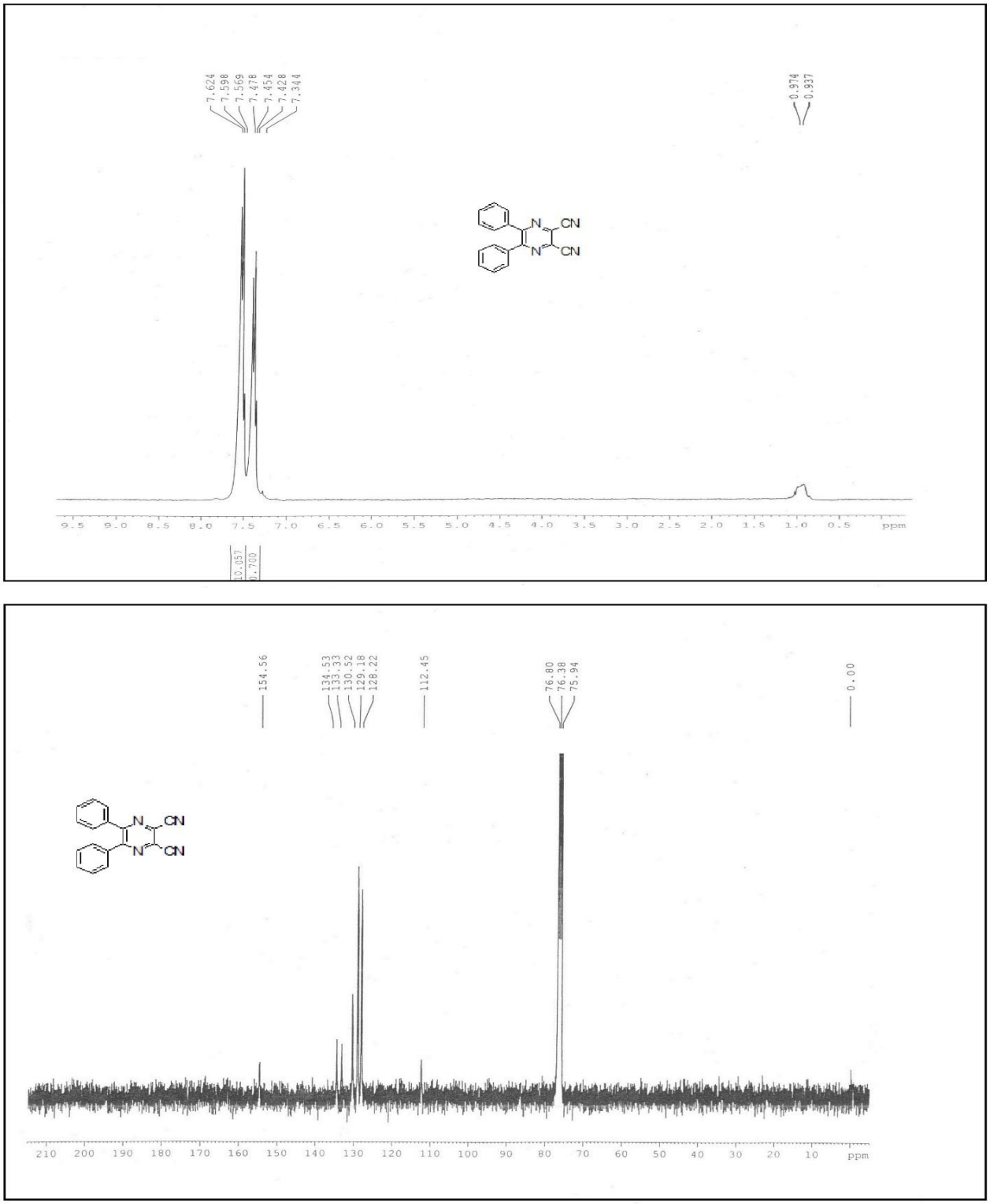


Fig. IV. B. 2. ^{1}H and ^{13}C NMR spectra of 5, 6-Diphenylpyrazine-2, 3-dicarbonitrile

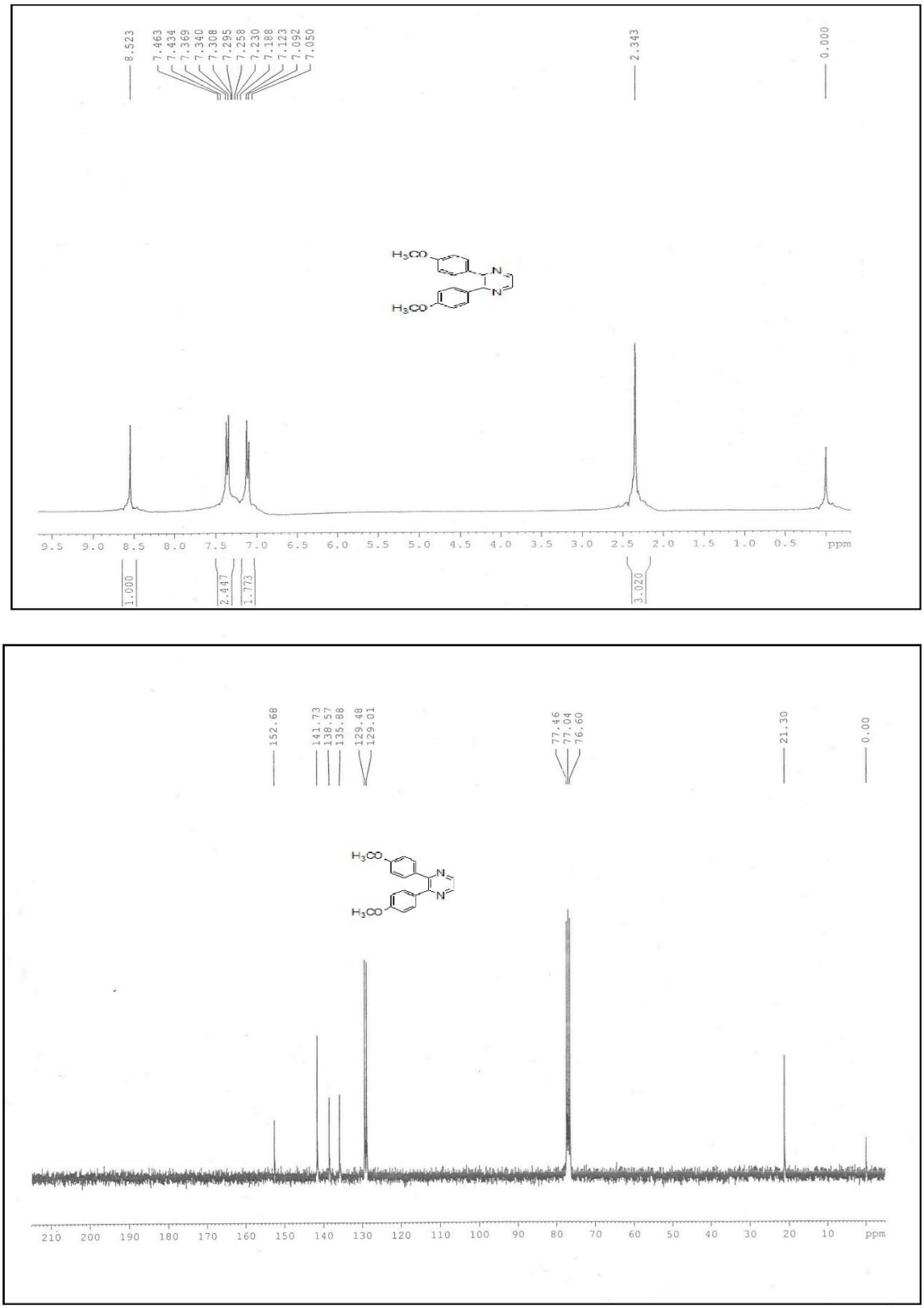


Fig. IV. B. 3. ^{1}H and ^{13}C NMR spectra of 2, 3-bis (4-methoxyphenyl) pyrazine

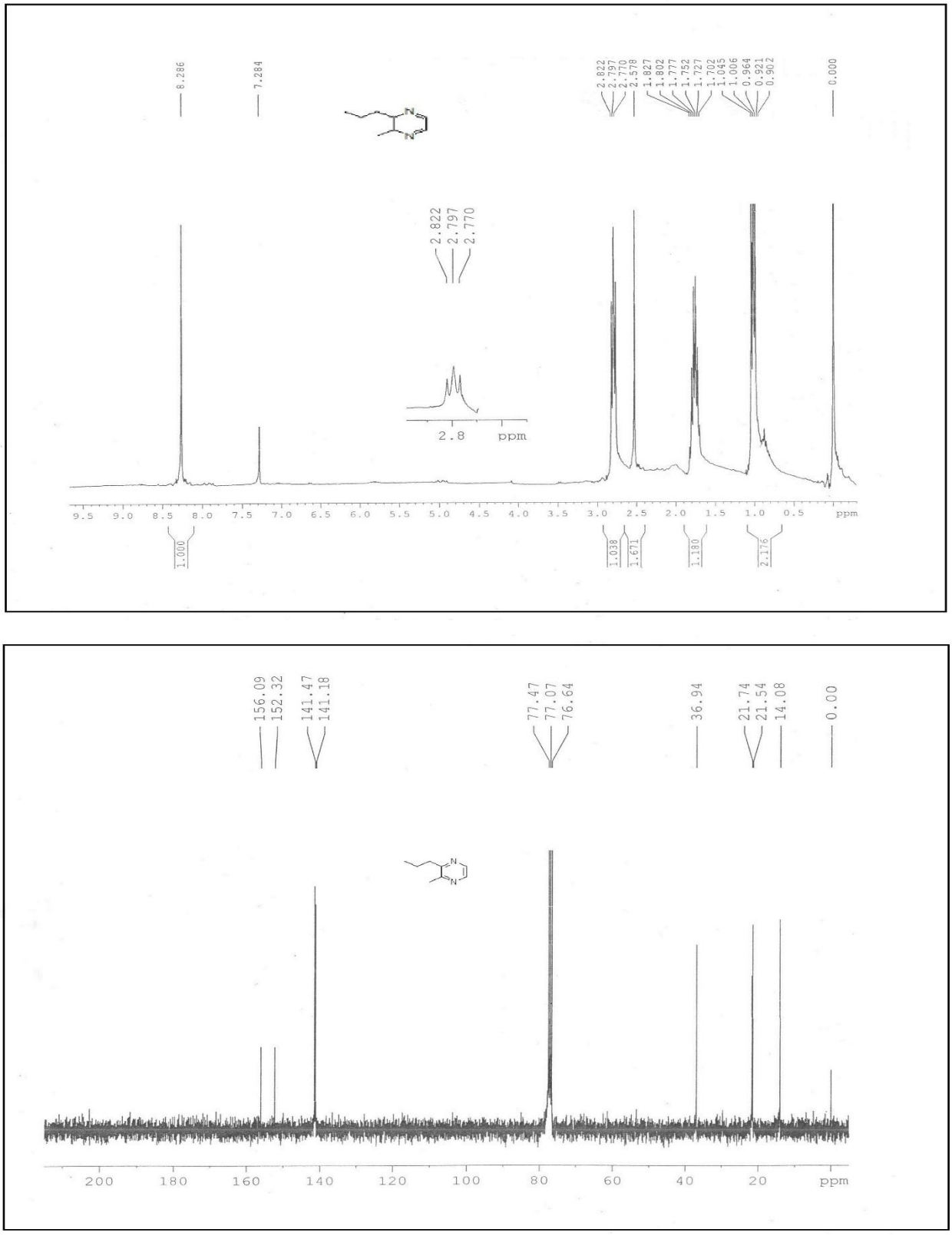


Fig. IV. B. 4. ^{1}H and ^{13}C NMR spectra of 2-Methyl-3-propylpyrazine

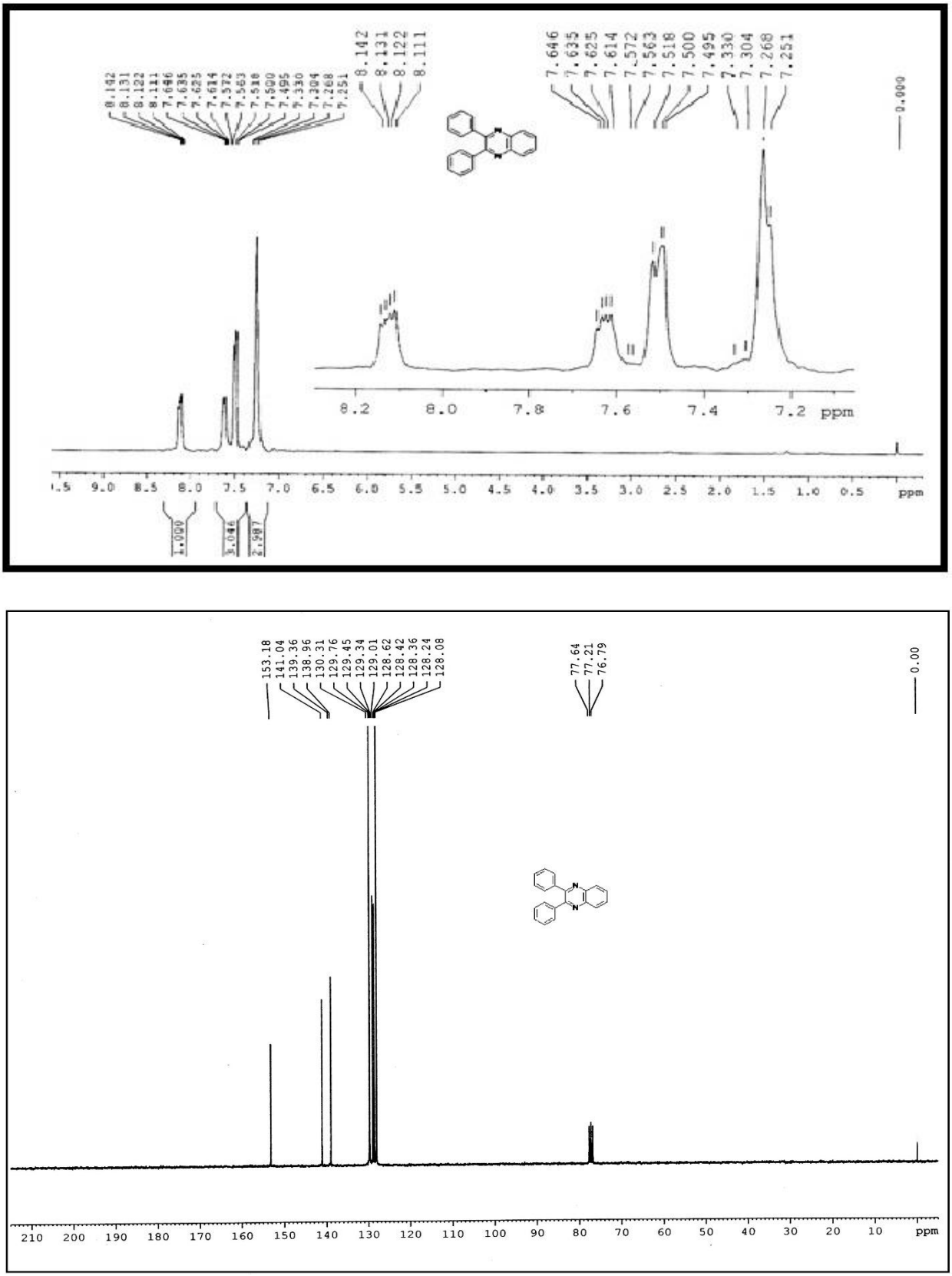


Fig. IV. B. 5. ^{1}H and ^{13}C NMR spectra of 2, 3-Diphenylquinoxaline

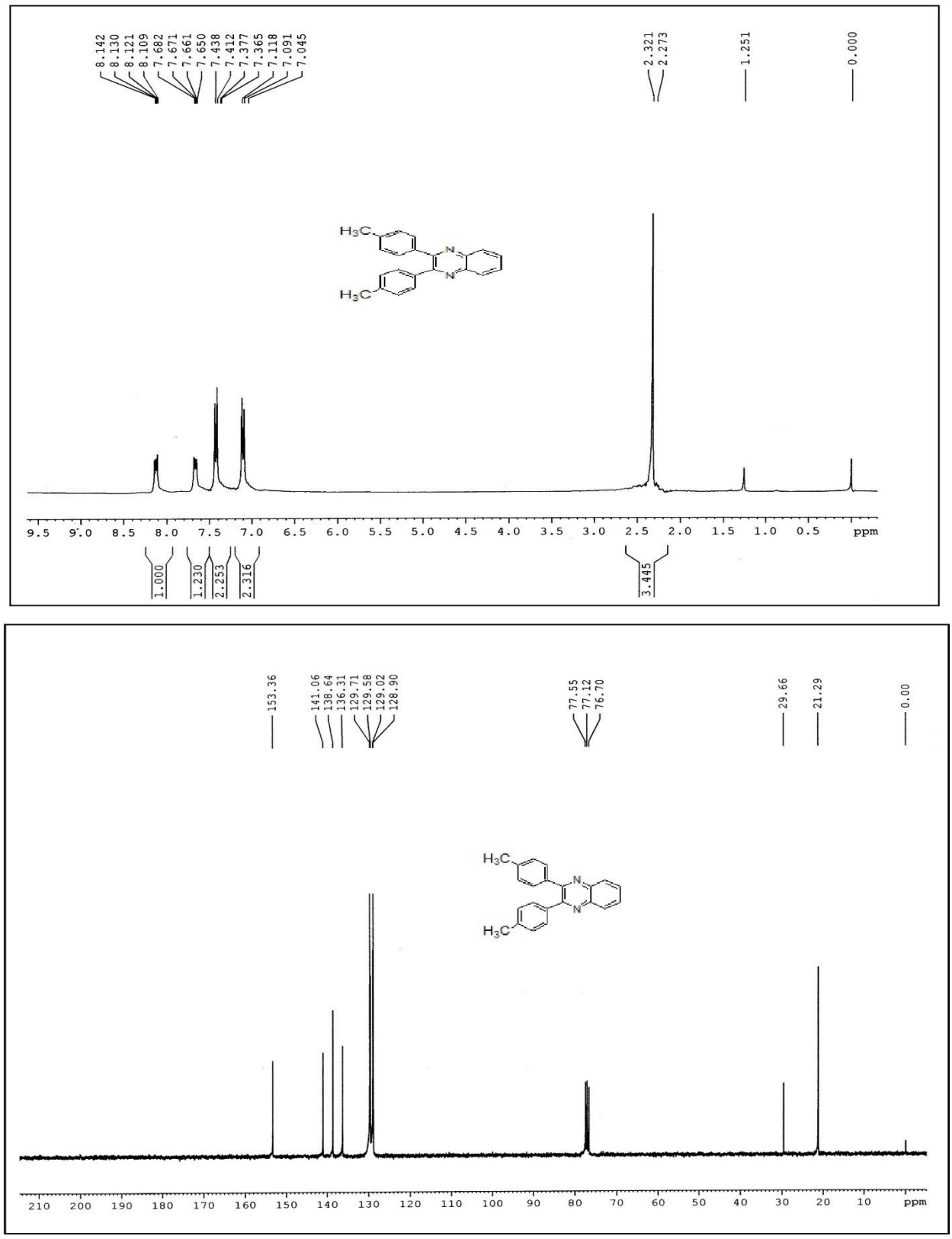


Fig. IV. B. 6. ^{1}H and ^{13}C NMR spectra of 2, 3-di-*p*-tolyl quinoxaline

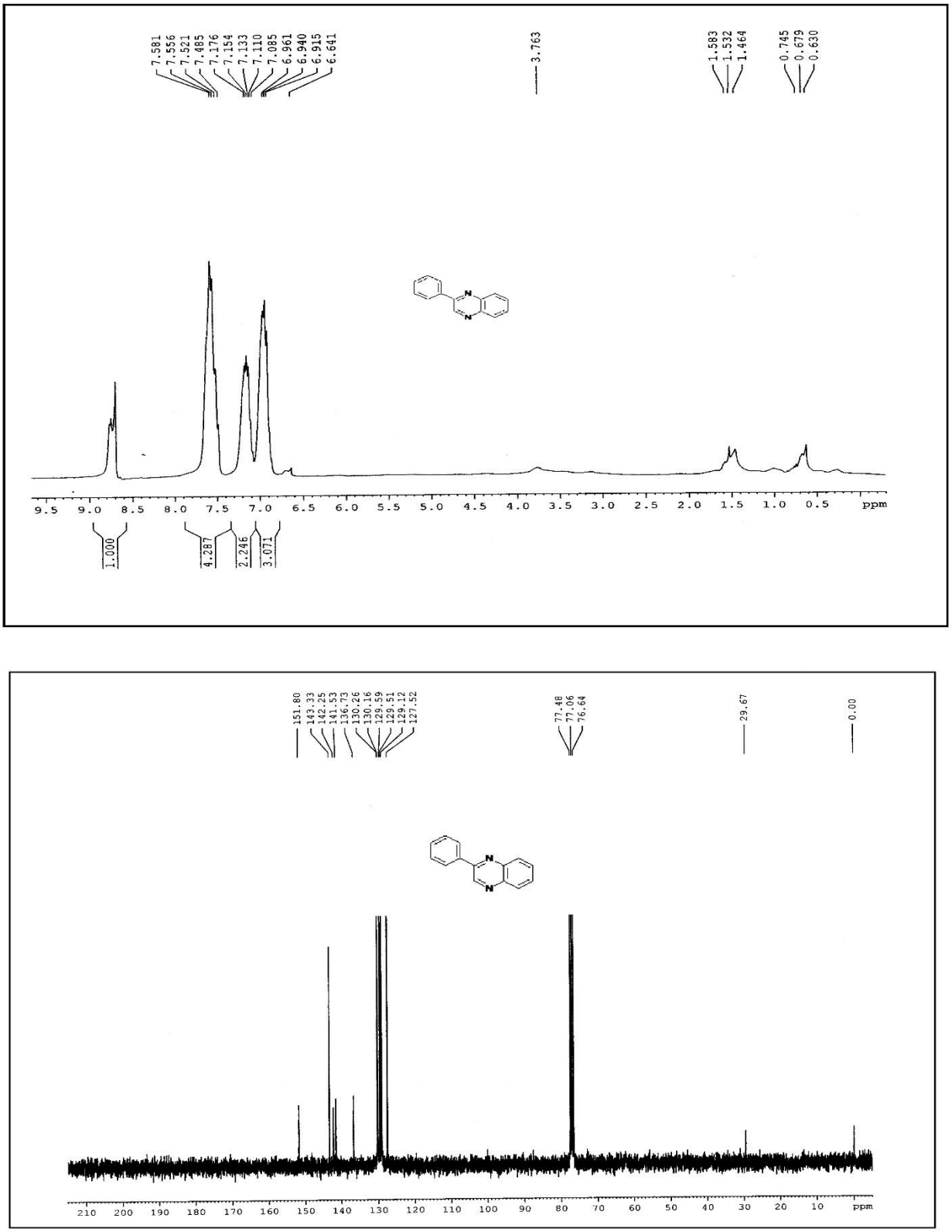


Fig. IV. B. 7. ^{1}H and ^{13}C NMR spectra of 2- phenyl quinoxaline

CHAPTER IV

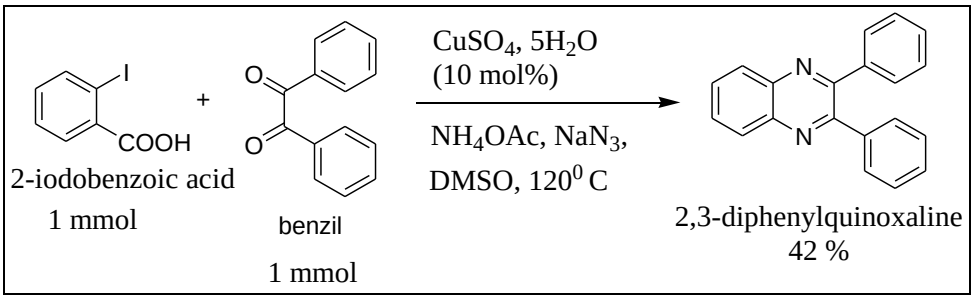
SECTION C

(Present investigation)

Preparation of quinoxaline from an unconventional and easily available precursor using polymeric Cu (II) catalyst through elimination and cyclization process

IV. C. 1. Result and discussion:

The conventional method for the preparation of quinoxaline is the condensation of aryl-1, 2-diamine and 1,2-diketone. Though several well accepted protocols are present for this condensation reaction rather there is always a drawback regarding to the oxidation of aryl-1, 2-diamine which lead an unexpected side product, also sometimes it gives a Schiff's base type side product, besides carcinogenicity and less stability of the diamine precursor makes a scope to switch it with other less toxic and easily available precursor for the process. Here we choose an unconventional precursor 2-iodobenzoic acid for the aryl skeleton of the quinoxaline moiety and benzil. In the endeavor of our investigation we choose benzil (1 mmol), 2-iodobenzoic acid (1 mmol), $CuSO_4$, $5H_2O$ (10 mol %), both NH_4OAc and NaN_3 (1 mmol for each) as a nitrogenous source in DMSO solvent (3 mL) at 120^0 C (scheme IV. C. 1). It gives around 42 % of yield of the required product, i.e., 2, 3-diphenyl quinoxaline after 9h.



Scheme IV. C. 1. Preparation of quinoxaline using 2-Iodobenzoic acid and benzil as a starting precursor

It encourages us to further investigate of our reaction protocol using our polymeric copper (II) catalyst (fig IV. C. 1, characterized by XRD and SEM images and has already discuss in the section B of chapter III).

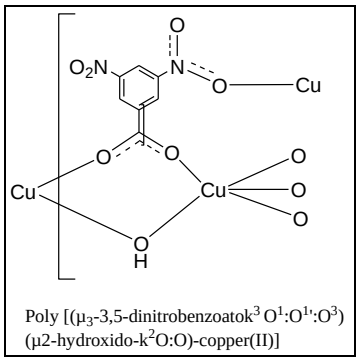
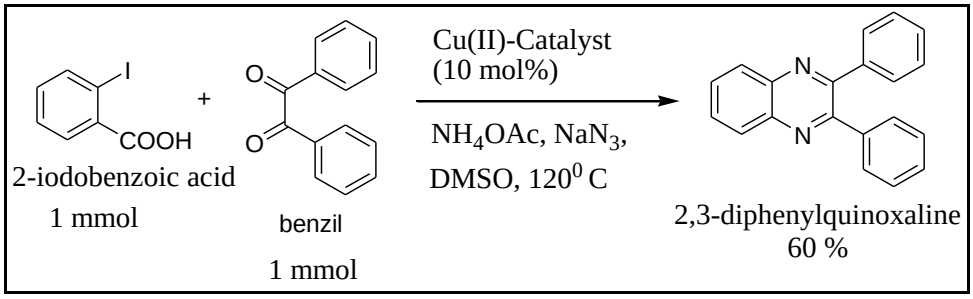


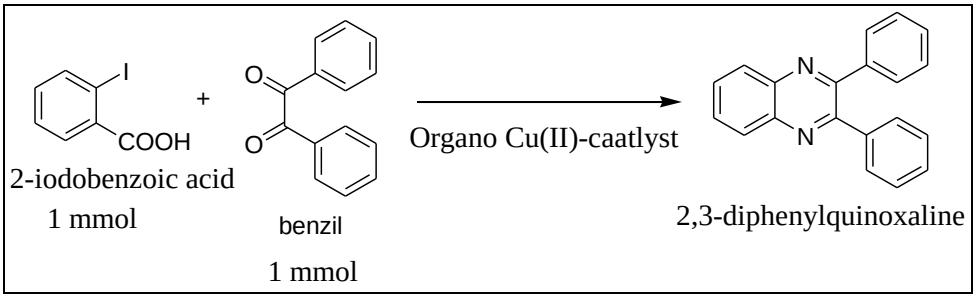
Fig IV. C. 1: General structure of the polymeric copper (II) catalyst.

We took polymeric Cu (II) catalyst (10 mol %) instead of $CuSO_4$, $5H_2O$ keeping other conditions same as before [i.e. benzil (1 mmol), 2-iodobenzoic acid (1 mmol), NH_4OAc and NaN_3 (1 mmol for each) for nitrogen source in DMSO (3 mL) at 120 ^{0} C; (scheme. IV. C. 2). A better yield of the desired product, i.e., 2, 3-diphenyl quinoxaline (60 % in 8h), encourages us for further investigation of the reaction protocol including optimization of the reaction condition. Further, on screening of the reaction protocol (table. IV. C. 1) we found that, benzil (1 mmol), 2-iodobenzoic acid (1.1 mmol), NH_4OH and NaN_3 (1 mmol for each) as nitrogenous source in DMSO (3 mL) at reflux condition is the optimized reaction condition (entry 14 of table. IV. C. 1). Next, we tried to find the superiority of the polymeric Cu (II) catalyst over other metal catalyst (table. IV. C. 2). It is found that though certain conventional Cu (II) catalyst gave the required product but the yield was poor.



Scheme. IV. C. 2. Preparation of quinoxaline using polymeric Cu (II)-catalyst

Table IV. C. 1: Optimization of reaction condition:



Entry	Cu (II) catalyst (mol %)	Nitrogenous source (1mmol)	NaN_3(1mmol)	Solvent (3mL)	Temp. (^{0} C)	Time (h)	Yield [a] (%)
1[b]	10	NH_4OAc	-	DMSO	120	8	60
2[b]	-	-	-	-	140	8	63
3[b]	-	-	-	-	reflux	6	72
4	-	-	-	DMF	-	10	35
5	5	-	-	DMSO	-	12	45
6	20	-	-	-	-	8	64
7	10	NH_4Cl	-	-	-	12	32
8	-	$(NH_4)_2SO_4$	-	-	-	10	nr [c]
9	-	NH_4F	-	-	-	12	-
10	-	$(NH_4)_2CO_3$	-	-	-	-	10
11	-	NH_4HCO_3	-	-	-	-	nr [c]
12	-	NH_4HF_2	-	-	-	-	nr [c]
13	-	HCO_2NH_4	-	-	-	-	nr [c]
14[d]	-	**NH_4OH**	-	-	-	**6**	**79**

15[e]	-	-		-	-	12	nr
16[f]		-	-	-	-	12	nr

[a]all yields are isolated yields, [b] reaction observed upto 12h no further improvement with respect to yield was obtained, [c] non-separable spots other than reactant was appeared in TLC,

[d] optimized reaction condition (reaction was also checked with increased amount of each NH_4OH and NaN_3 upto 2 mmol but no further improvement in the yield was observed),

[e] reaction was done in absence of NaN_3 using 2 mmol of NH_4OH, [f] reaction was done without catalyst.

Table IV. C. 2: Comparing effectiveness of polymeric Cu (II)-complex with other metal salt under our optimized reaction condition [a]:

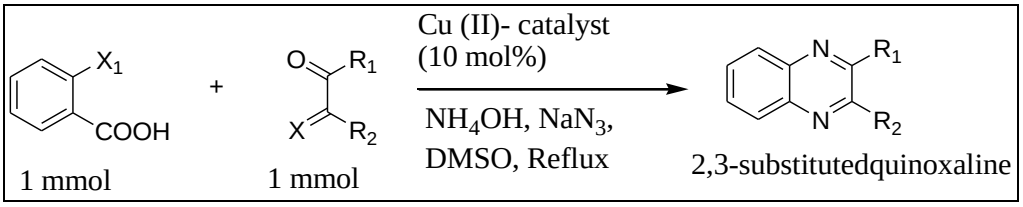
Entry	Catalyst[d] (mol %)	Time (h)	Yield [b] (%)
1	polymeric Cu(II)-complex	6	79
2 [c]	$CuSO_4$	8	55
3 [c]	$CuCl_2$	10	35
4	$Cu(OAc)_2$	10	nr
5[c]	$CuBr_2$	10	15
6	$Cu(NO_3)_2$	12	nr
7	CuI	-	-
8	CuCl	-	-
9	CuBr	-	-
10	$FeCl_3$	-	-

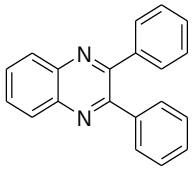
11	$Zn(OAc)_2$	-	-
12	$CoCl_2$	-	-
13	$MnSO_4$	-	-
14	$NiCl_2$	-	-

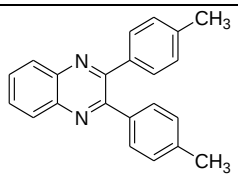
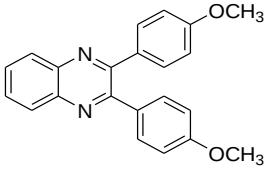
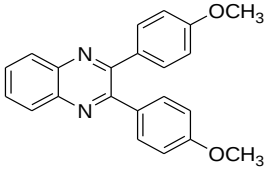
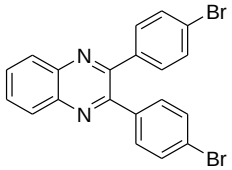
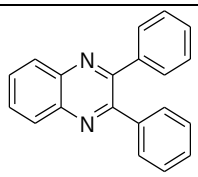
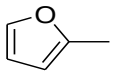
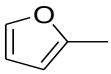
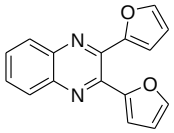
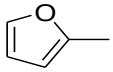
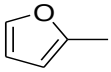
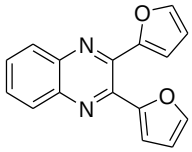
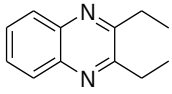
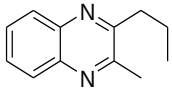
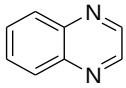
[a]benzil (1mmol), 2-iodobenzoic acid (1mmol), NH_4OH (1mol%) and NaN_3 (1 mmol) in DMSO (3 mL) under reflux condition, [b] yields are isolated yields, [c] all reaction was checked upto 12h but no further change in product yield was observed after the reported time, [d] 10 mol% catalyst was taken for each reaction.

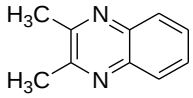
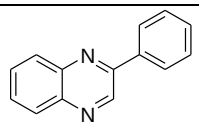
After achieving a suitable optimized condition for the reaction, further we used some substituted *vic*-diketone/α-hydroxy ketone and try to check the applicability of our newly developed protocol (table. IV. C. 3). From, the results it is clear that our reaction protocol is well applicable for aromatic *vic*-diketone/α-hydroxy ketone (entry 1-8 in table. IV. C. 3) and also for phenacyl bromide (entry 13 in table. IV. C. 3), but in case of aliphatic *vic*-diketone (entry 11 and 12 in table. IV. C. 3) the yield was poor due to their volatile nature. However, we were unable to find any suitable protocol for chloro or bromo substituted benzoic acid precursor (entry 14 and 15 in table. IV. C. 3).

Table IV. C. 3: Preparation of substituted quinoxaline using various ketones under our optimized condition[a]:



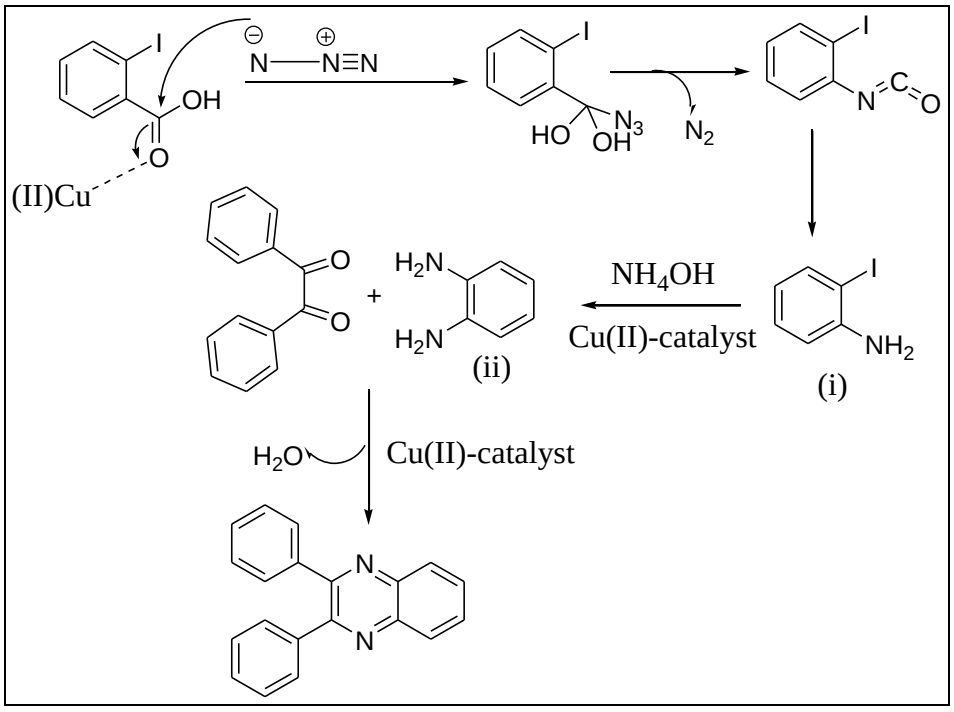
Entry	R1	R2	X	X_1	Time (h)	Product	Yield [b] (%)
1	-Ph	-Ph	O	I	6		79

2	*p*CH_3-C_6H_5-	*p*CH_3-C_6H_5-	-	-	$6^{1/2}$		72
3	*p*CH_3O-C_6H_5	*p*CH_3O-C_6H_5	-O	-	6		70
4	*p*CH_3O-C_6H_5	*p*CH_3O-C_6H_5	-OH	-	$6^{1/2}$		65
5	pBr-C_6H_5	*p*Br-C_6H_5	-	-	7		62
6	-Ph	-Ph	-OH	-	6		75
7			O	-	8		71
8			-OH	-	$8^{1/2}$		72
9^c	$-C_2H_5$	$-C_2H_5$	-	-	7		68
10^c	$-C_3H_7$	$-CH_3$	-	-	7		65
11^d	-H	-H	O	-	6		10

12[d]	$-CH_3$	$-CH_3$	O	-	$6^{1/2}$		35
13[e]	-Ph	-H	Br	-	8		55
14	-Ph	-Ph	O	Cl	10		nr
15	-	-	-	Br	10		nr

[a]*vic*-diketone/α-hydroxy ketone (1mmol), 2-iodobenzoic acid (1mmol), polymeric Cu (II)-catalyst (10 mol %), NH_4OH (1 mol%) and NaN_3 (1 mmol) in DMSO (3 mL) under reflux condition, [b] yields are isolated yields, [c] 1.5 mmol *vic*-diketone was used, [d] 2 mmol *vic*-diketone was used, [e] Na_2CO_3 (1equiv) was used during the reaction.

Finally, we tried to give a plausible mechanism for the polymeric Cu (II)-catalyzed conversion of quinoxaline from benzil and 2-idobenzoic acid is shown in (Scheme IV. C. 3). We believe that initially the reaction proceeds through Schmidt reaction mechanism to yield the intermediate (i). Which then subsequently produce another intermediate (ii). Reactions of (ii) with diketo compound finally produce the desired product.



Scheme IV. C. 3. Plausible mechanism of the reaction

IV. C. 2. Experimental:

Scanning electron micrograph of the synthesized copper (II) complex has been recorded using Inspect F-50 FEI scanning electron microscope with SEM accelerating voltage of 10.00 kV and magnification of 20000X. ^{1}H NMR and ^{13}C NMR were recorded on Bruker Advance FT-NMR (300 MHz) Spectrometer using TMS as internal standard.

IV. C. 2.1. Reaction procedure:

IV. C. 2.1 1. General procedure for the preparation of Cu II-Catalyst:

A mixture of 3, 5-dinitrobenzoic acid (0.1688 g), $Cu(NO_3)_2.3H_2O$ (0.1932 g) and melamine (0.1002 g) was taken and grinded to dust in a mortar pistol. To the mixture 1.5 mL of distilled water was added and stirred for 30 min until we get a suspension. Then the reaction mixture was sealed in a 10 ml Teflon-lined stainless-steel autoclave and heated for 45 h at 423 K. After that the autoclave was subjected to cooling (for 5 h) to room temperature. The reaction mixture was filtered and was subsequently washed with distilled water. We get blue colored crystal of the product, which was further characterized by single crystal X-ray diffraction and SEM data.

IV. C. 2.1. 2. General Process for the preparation of 2, 3-disubstituted quinoxaline:

A mixture of substituted *vic*-diketone/α-hydroxy ketone (1mmol), 2-iodobenzoic acid (1mmol), polymeric Cu (II)-catalyst (10 mol %), NH_4OH (1 mol %) and NaN_3 (1 mmol) in DMSO (3 mL) was taken in a 50mL round bottom flask and refluxed for specified time (Table. IV. C. 3). The progress of reaction was monitored by TLC. After the completion of the reaction the product was extracted with ethyl acetate and further purified by column chromatography using silica gel 60-120 mesh.

IV. C. 2. 2. Chemicals:

All the chemicals used in this investigation including their purity and sources are summarized in the following table (table. IV. C. 4).

Table IV. C. 4: Chemicals used for present investigation

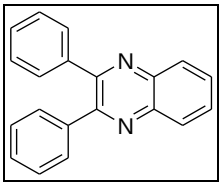
Entry	Chemicals	Sources	Purity (%)
1	4, 4'-Dimethyl benzil	Sigma-Aldrich	97
2	4,4'-Dimethoxy benzil	Sigma-Aldrich	98
3	4,4'-Dibromo benzil	Sigma-Aldrich	90
4	Glyoxal	SRL	-
5	2,3-Hexadione	Sigma-Aldrich	90
6	3,4-Hexadione	Sigma-Aldrich	95
7	Diacetyl	S.D. Fine	-
8	Furil	Sigma-Aldrich	98
9	Furoin	Sigma-Aldrich	98
10	$CDCl_3$for NMR	S.D. Fine	97
11	Petroleum ether	Thomas Baker	98
12	Ethyl acetate	Thomas Baker	99
13	Silica-gel 60-120 mesh for column	SRL	-
14	Silica-gel for TLC	SRL	-
15	Na_2SO_4anhydrous	SRL	99.5
16	Benzil	SRL	98
17	3,5-Dinitrobenzoic acid	Sigma-Aldrich	99
18	$Cu(NO_3)_2.3H_2O$	SRL	99.5
19	Melamine	Sigma-Aldrich	99

IV. C. 3. Conclusion:

From the above study, it can be concluded that, using the developed protocol, 2, 3-disubstituted quinoxaline can easily be synthesized from different diketone sources in presence of an unconventional precursor 2-idobenzoic acid through a mild reaction condition. By this, we have explored an alternative methodology for the preparation quinoxaline without using 1,2-aryl diamine source.

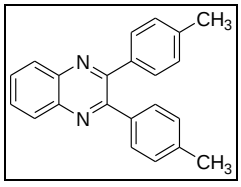
IV. C. 4. Spectral data:

IV. C. 4. 1. 2, 3-Diphenylquinoxaline:



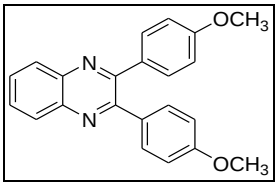
^{1}H NMR ($CDCl_3$, 300MHz): 7.25-7.33 (m, 6H), 7.50-7.65 (m, 6H), 8.11-8.14 (m, 2H); ^{13}C NMR ($CDCl_3$, 75MHz):128.1, 128.6, 129.0, 129.8, 138.9, 141.0, 153.2 ppm.

IV. C. 4. 2. 2, 3-Di-*p*-tolylquinoxaline:



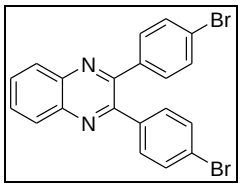
^{1}H NMR ($CDCl_3$, 300MHz): 2.32 (s, 6H), 7.10 (d, 4H, *J* = 8.1 Hz), 7.43 (d, 4H, *J* = 7.8 Hz), 7.65-7.68 (dd, 2H, *J* = 3.3 and 6.3 Hz), 8.11-8.14 (dd, 2H, *J* = 3.3 and 6.3 Hz); ^{13}C NMR ($CDCl_3$, 75MHz): 21.3, 128.9, 129.0, 129.6, 129.7, 136.3, 138.6, 141.1 ppm.

IV. C. 4. 3. 2, 3-Bis (4-methoxyphenyl) quinoxaline:



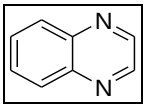
^{1}H NMR ($CDCl_3$, 300MHz): 3.83 (s, 6H), 6.87 (d, 4H, *J* = 8.4 Hz), 7.49 (d, 4H, *J* = 8.7 Hz), 7.70-7.73 (dd, 2H, *J* = 3.6 and 6.3 Hz), 8.11-8.14 (dd, 2H, *J* = 3.6 and 6.3 Hz); ^{13}C NMR ($CDCl_3$, 75MHz): 55.3, 113.8, 129.0, 129.6, 131.3, 131.8, 141.1, 153.0, 160.2 ppm.

IV. C. 4. 4. 2, 3-Bis (4-bromophenyl) quinoxaline:



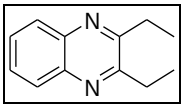
^{1}H NMR ($CDCl_3$, 300MHz): 7.38 (d, 4H, *J* = 8.1 Hz), 7.48 (d, 4H, *J* = 8.4 Hz), 7.78-7.75 (dd, 2H, *J* = 6.3 and 3.3 Hz), 8.12-8.15 (dd, 2H, *J* = 6.3 and 3.3 Hz); ^{13}C NMR ($CDCl_3$, 75MHz): 123.7, 129.1, 130.4, 131.4, 131.6, 137.6, 141.1, 151.8 ppm.

IV. C. 4. 5. Quinoxaline:



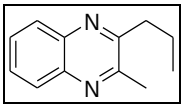
^{1}H NMR ($CDCl_3$, 300MHz): 7.70 (m, 2H), 8.07-8.11 (m, 2H), 8.81-8.84 (m, 2H); ^{13}C NMR ($CDCl_3$, 75MHz): 129.4, 130.0, 142.9, 144.9 ppm.

IV. C. 4. 6. 2, 3-Diethylquinoxaline:



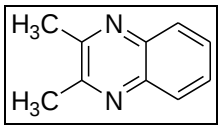
^{1}H NMR ($CDCl_3$, 300MHz): 1.43 (t, 6H, *J* = 7.5 Hz), 3.01-3.08 (q, 4H, *J* = 7.5 Hz), 7.63-7.66 (dd, 2H, *J* = 3.3 and 6.3 Hz), 8.00-8.04 (dd, 2H, *J* = 3.3 and 6.3 Hz); ^{13}C NMR ($CDCl_3$, 75MHz): 12.5, 28.3, 128.6, 141.0, 157.2 ppm.

IV. C. 4. 7. 2-Methyl-3-propylquinoxaline:



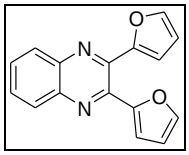
^{1}H NMR ($CDCl_3$, 300MHz): 1.09 (t, 3H, *J* = 7.2 Hz), 1.81-1.91 (sextet, 2H, *J* = 7.5 Hz), 2.77 (s, 3H), 2.95-3.00 (t, 2H, *J* = 7.5 Hz), 7.64-7.68 (m, 2H), 7.97-8.03 (m, 2H); ^{13}C NMR ($CDCl_3$, 75MHz): 14.2, 21.5, 22.8, 37.8, 128.2, 128.5, 128.8, 128.9, 140.8, 141.1, 153.2, 156.7 ppm.

IV. C. 4. 8. 2, 3-Dimethylquinoxaline:



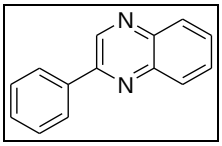
^{1}H NMR ($CDCl_3$, 300MHz): 2.71 (s, 6H), 7.63-7.66 (dd, 2H, *J* = 3.3, 6.3 Hz), 7.95-7.99 (dd, 2H, *J* =3.3, 6.3 Hz); ^{13}C NMR ($CDCl_3$, 75MHz): 23.1, 128.3, 128.8, 141.0, 153.4 ppm.

IV. C. 4. 9. 2, 3-Di (furan-2-yl)-quinoxaline:



^{1}H NMR ($CDCl_3$, 300MHz): 6.55-6.70 (m, 4H), 7.47-7.62 (m, 3H), 7.92-8.04 (m, 2H); ^{13}C NMR ($CDCl_3$, 75MHz): 21.8, 111.8, 112.5, 127.9, 128.5, 132.7, 139.0, 140.6, 140.9, 141.7, 142.5, 143.9, 144.0, 150.9 ppm.

IV. C. 4. 10. 2-Phenyl quinoxaline:



^{1}H NMR ($CDCl_3$, 300 MHz): 6.91-6.96 (m, 3H), 7.08-7.17 (m, 2H), 7.48-7.58 (m, 4H), 8.75 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): 127.5, 129.1, 129.5, 129.6, 130.1, 136.7, 141.5, 142.2, 143.3, 151.8 ppm.

IV. C. 5. Supporting Spectra:

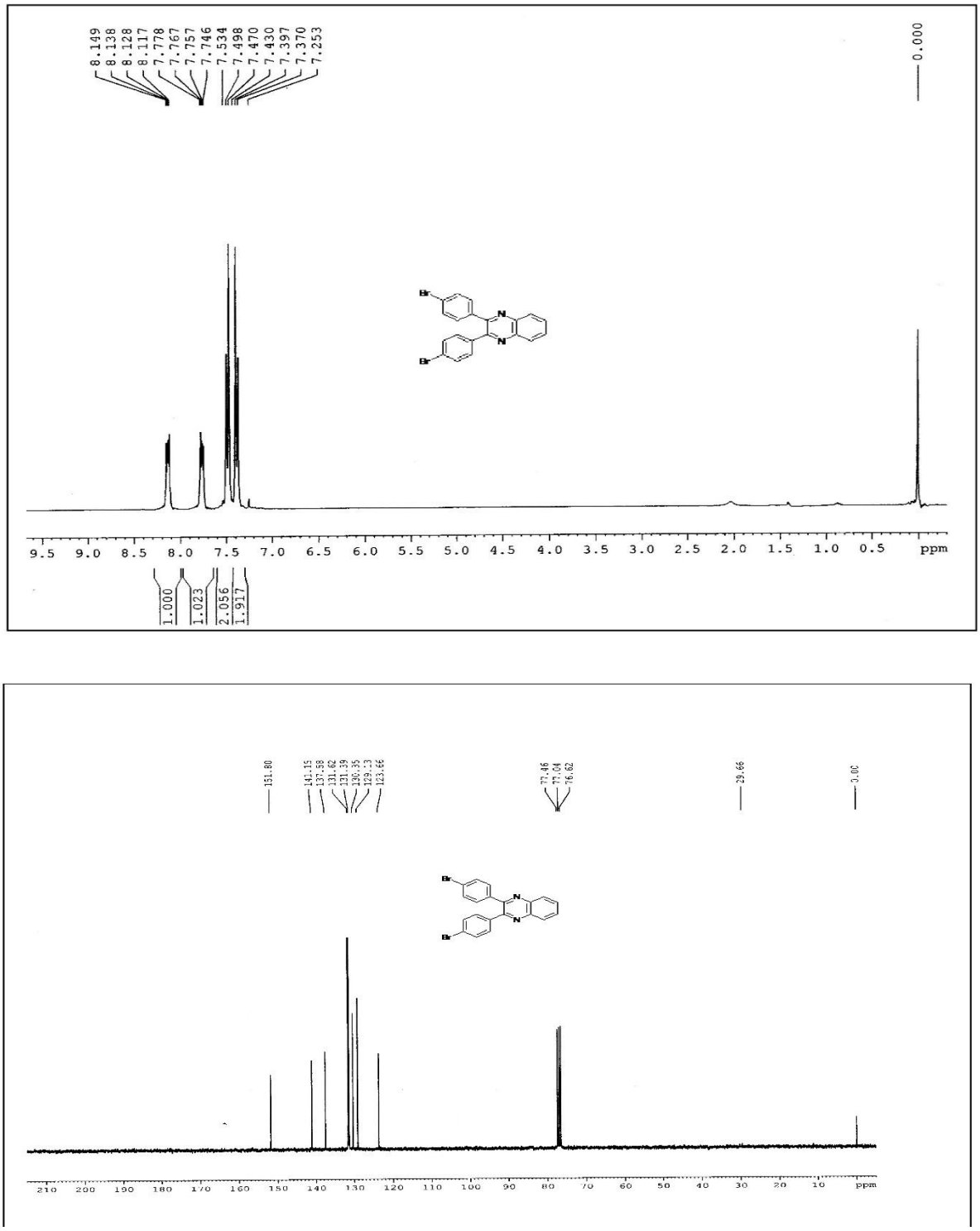


Fig. IV. C. 2. ^{1}H and ^{13}C NMR spectra of 2,3-Bis (4-bromophenyl) quinoxaline

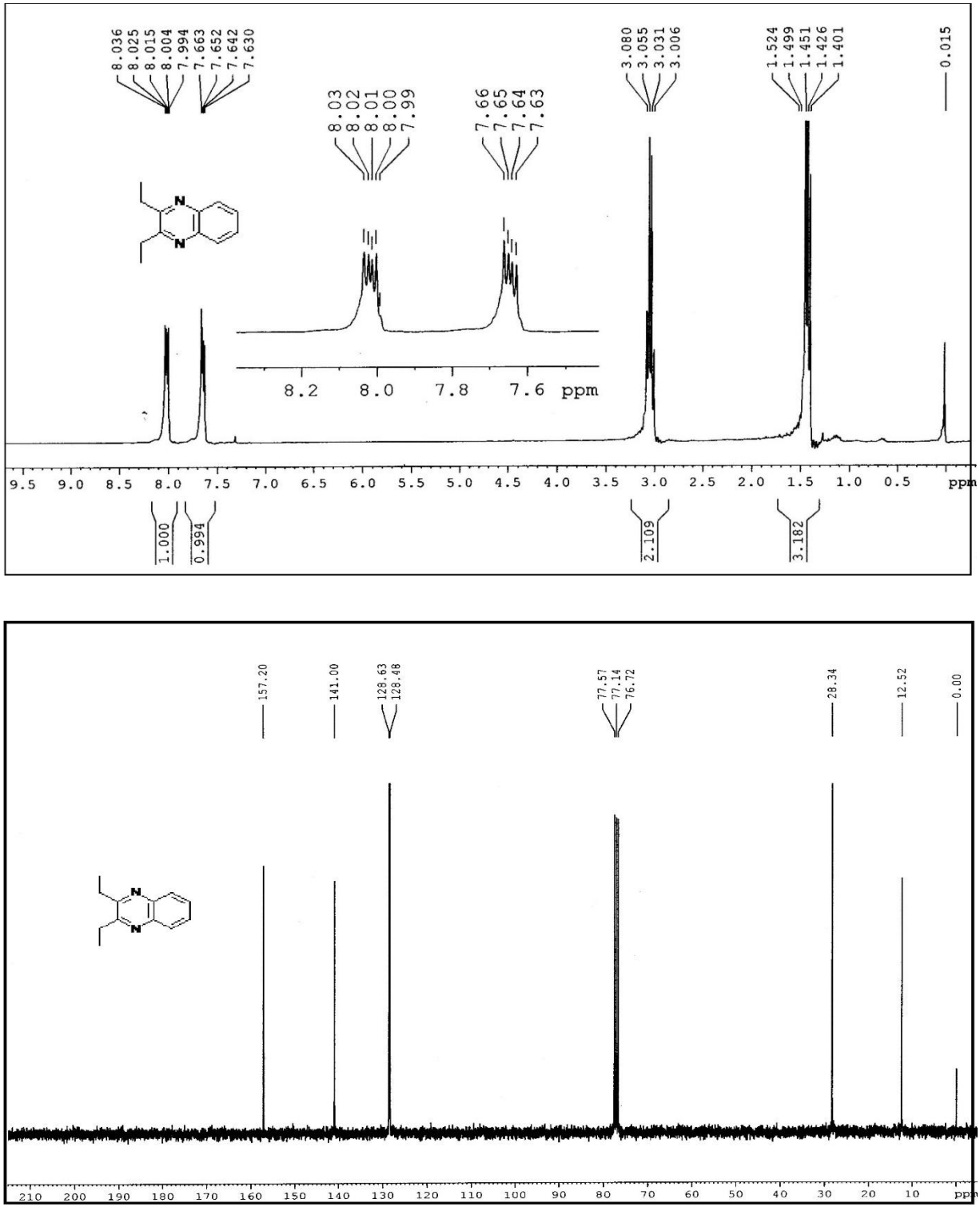
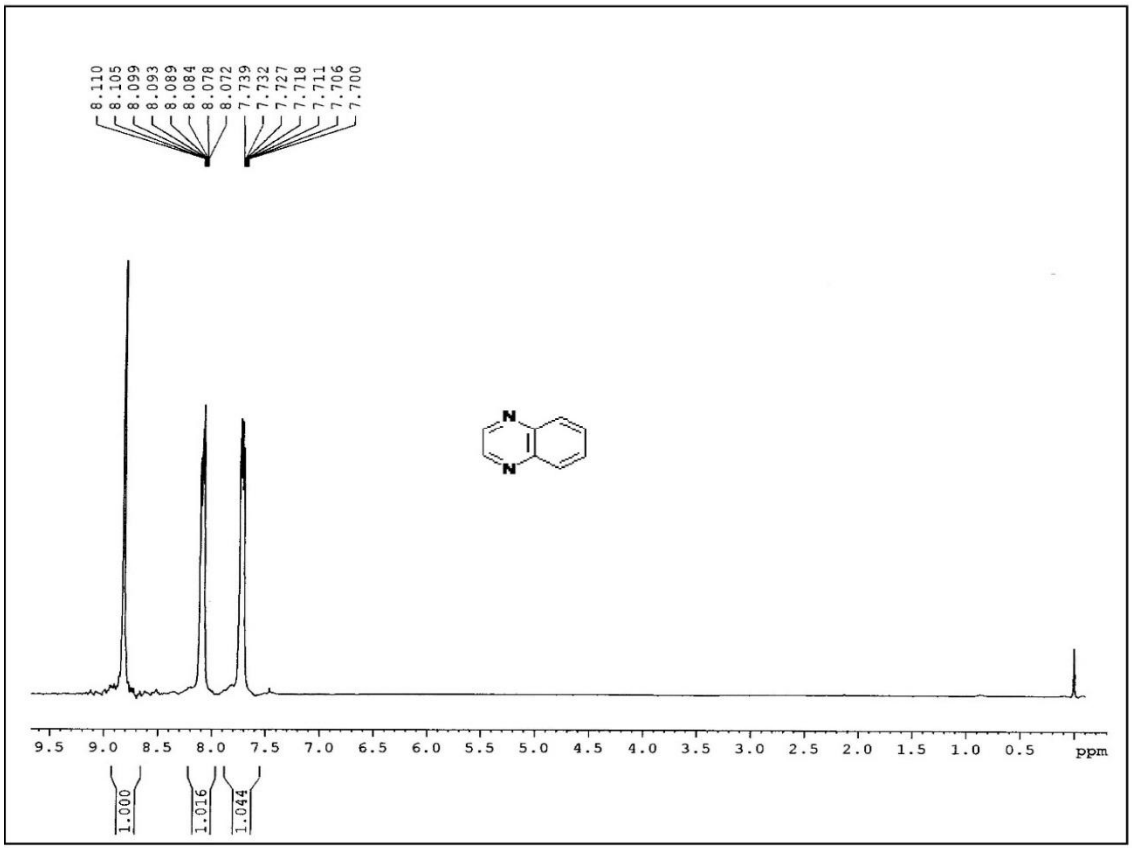


Fig. IV. C. 3. ^{1}H and ^{13}C NMR spectra of 2, 3-diethyl quinoxaline



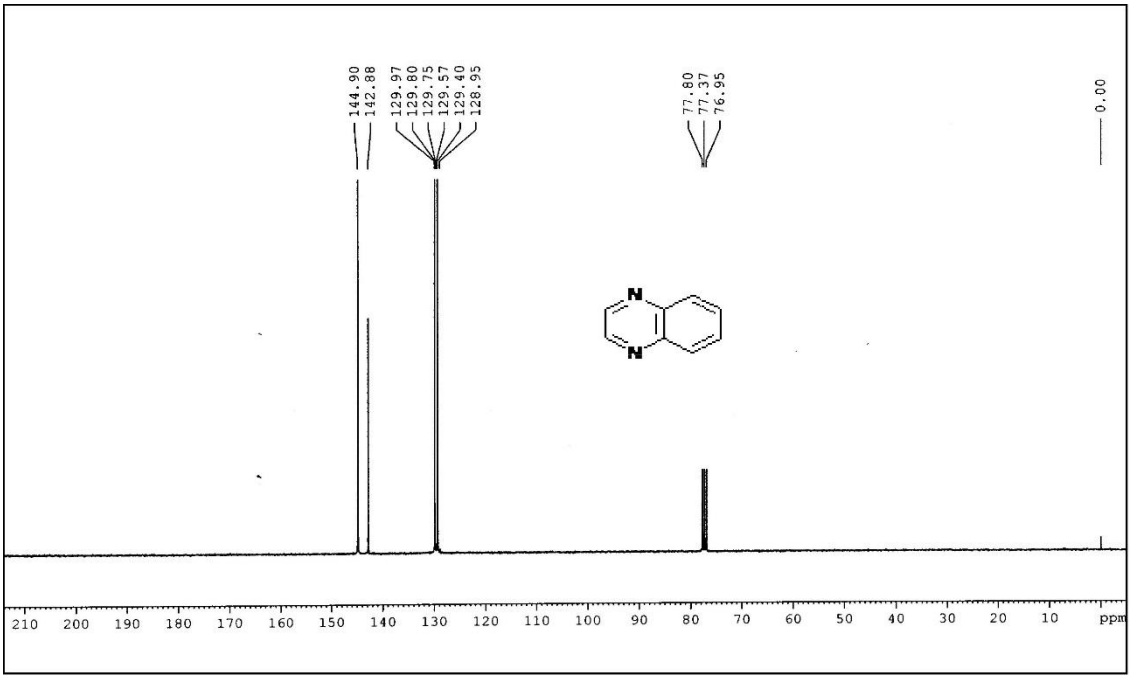


Fig. IV. C. 4.^{1}H and ^{13}C NMR spectra of quinoxaline

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Chapter IV

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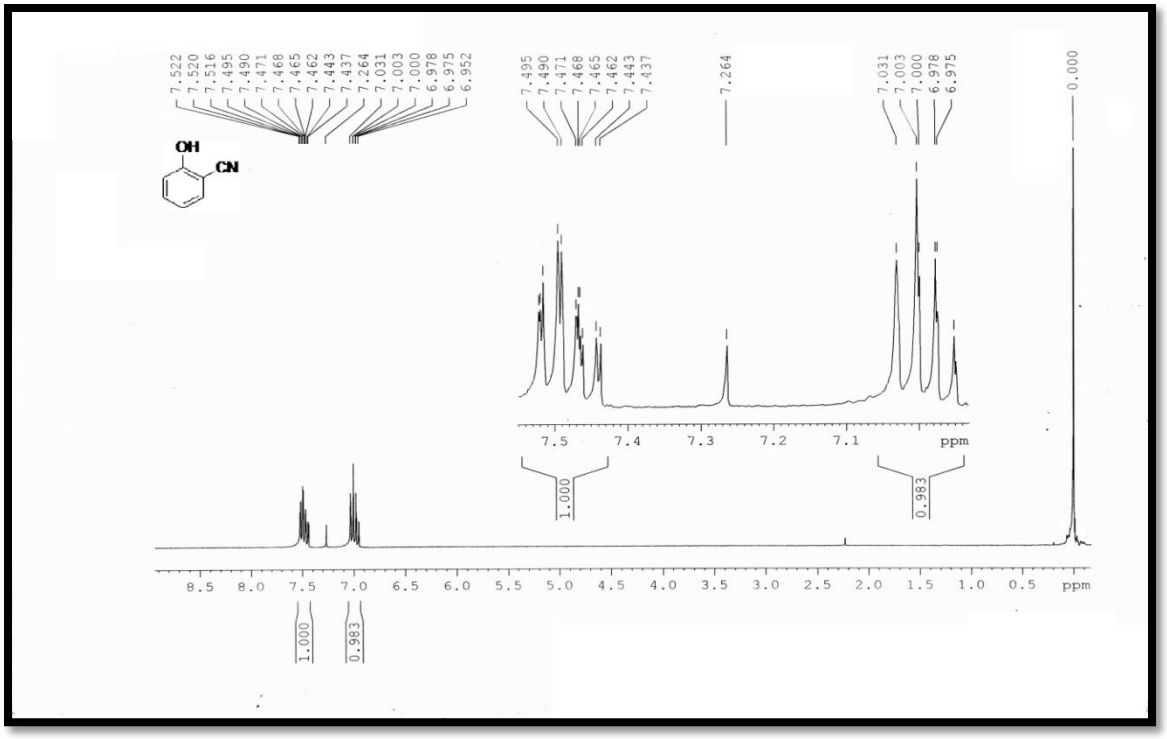
NMR SPECTRA OF ALL SYNTHESIZED COMPOUNDS [CHAPTER II TO IV]



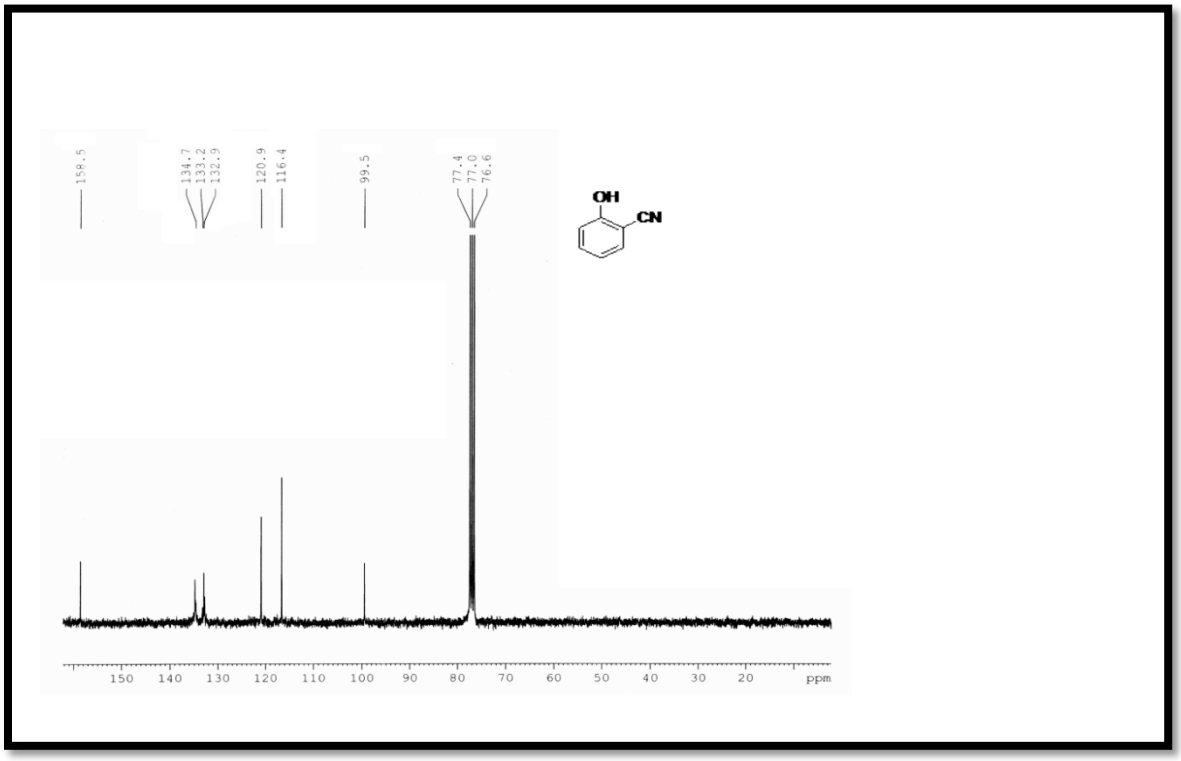
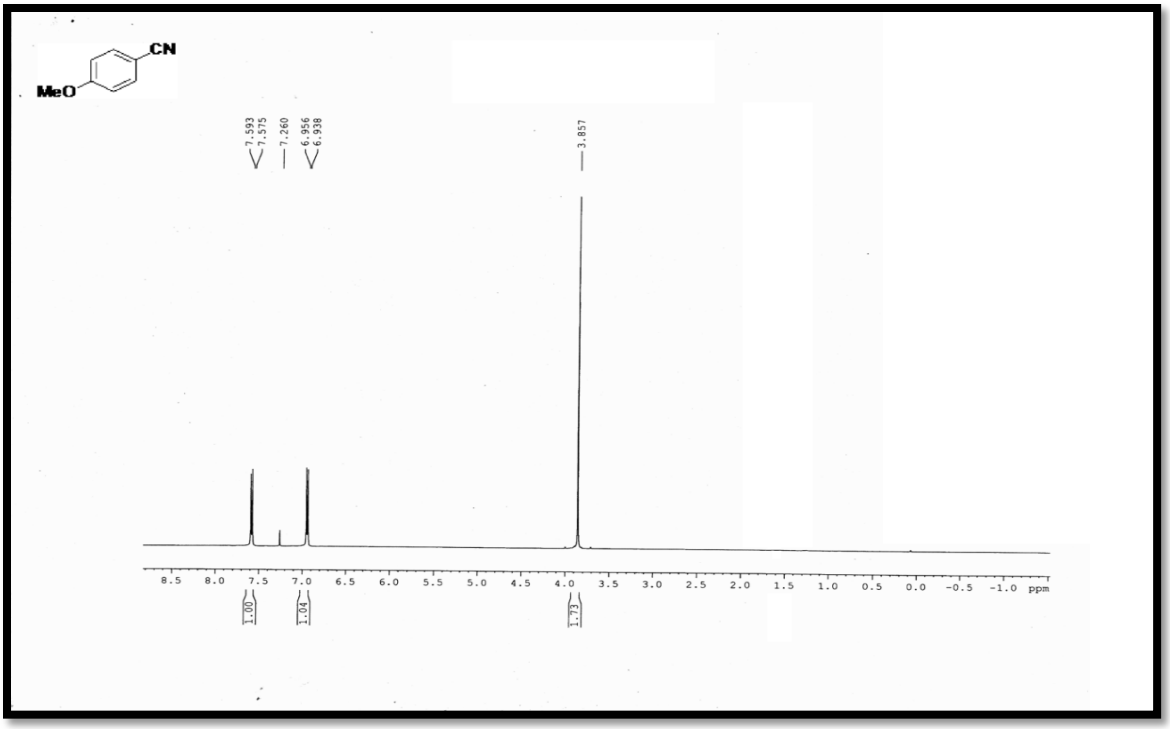
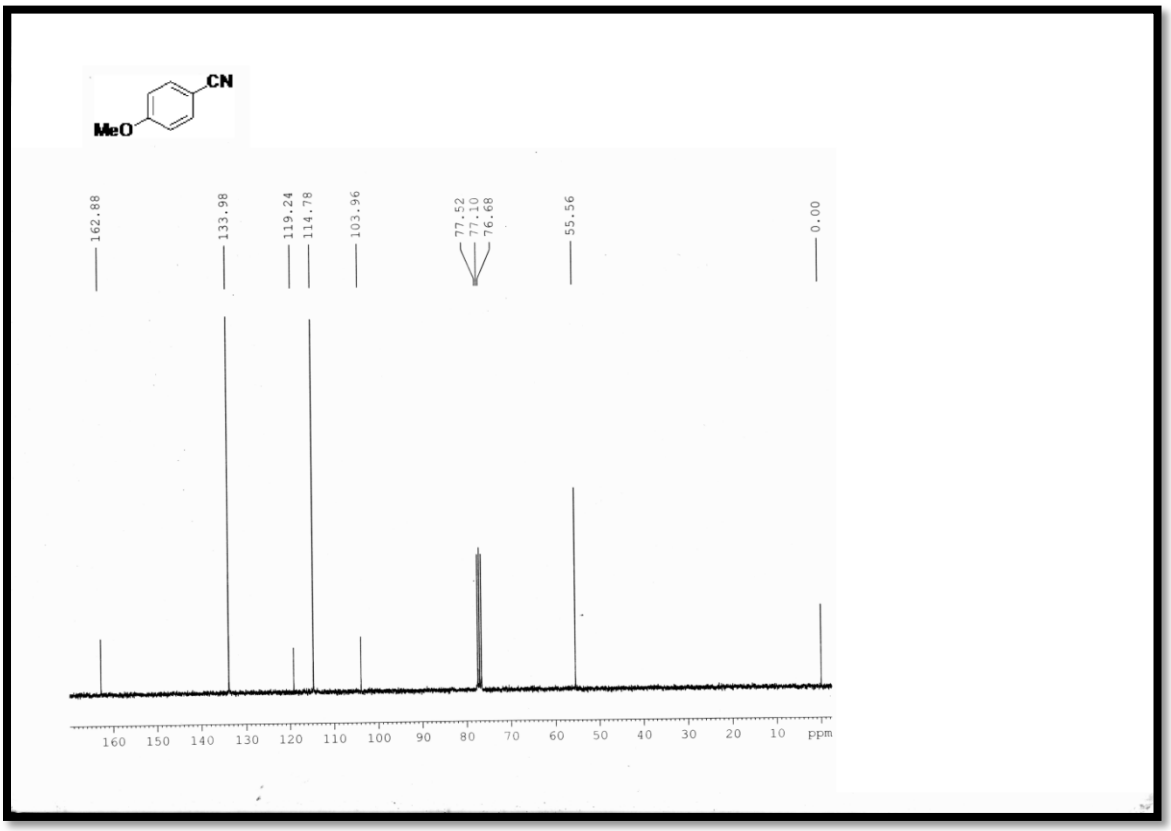


Fig. II. B. 8. ^{1}H and ^{13}C NMR of 2-Hydroxy-benzonitrile





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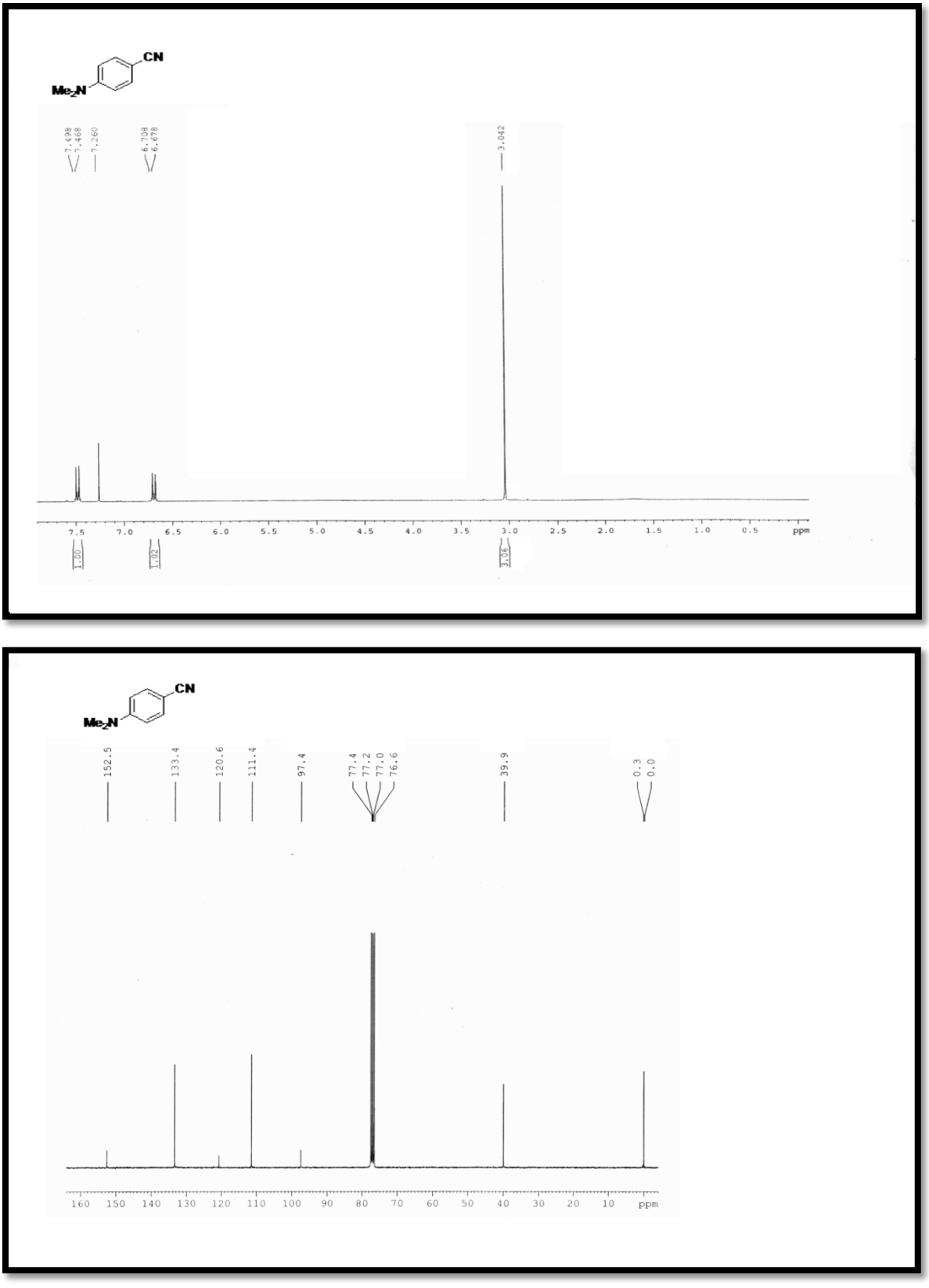

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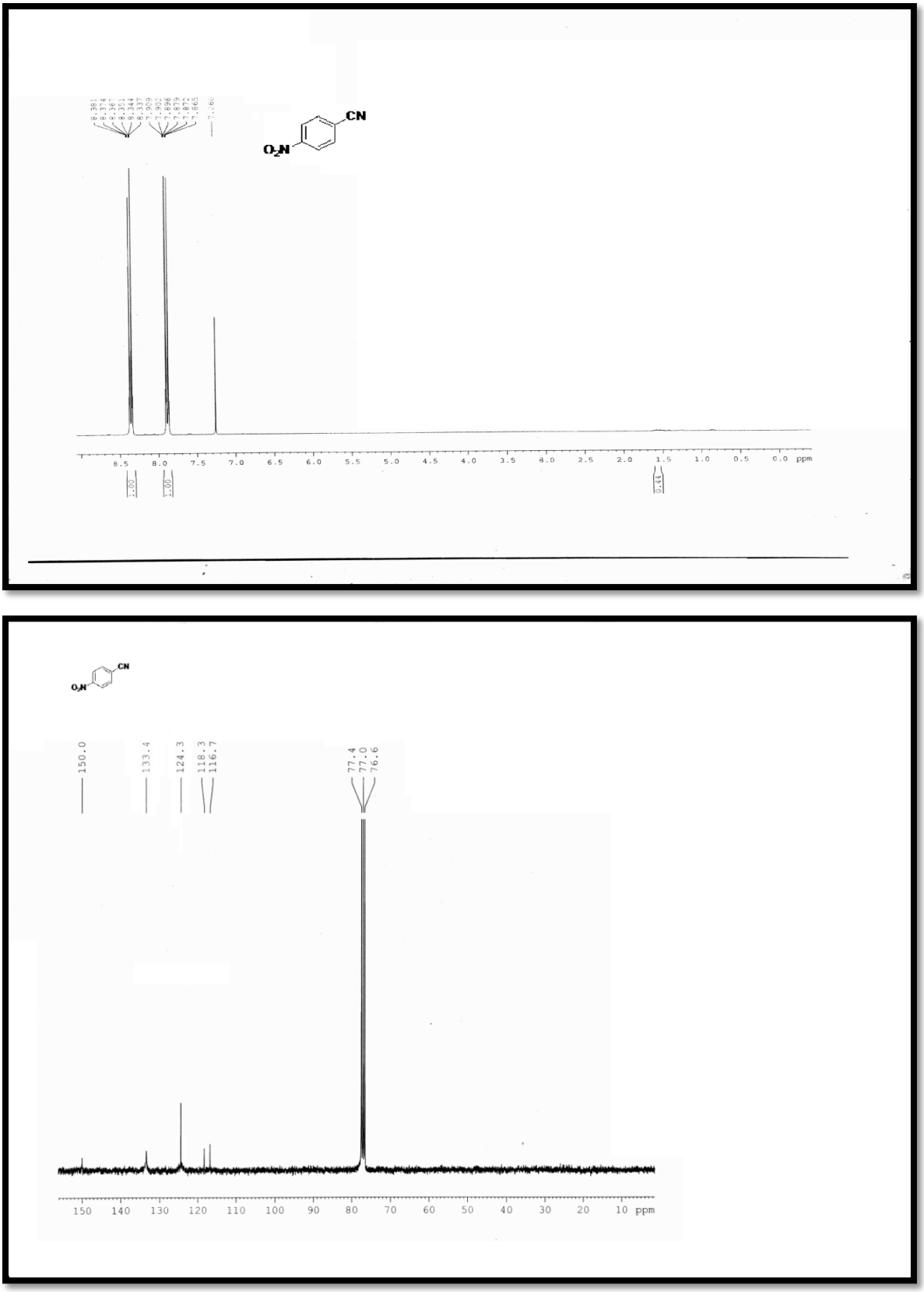

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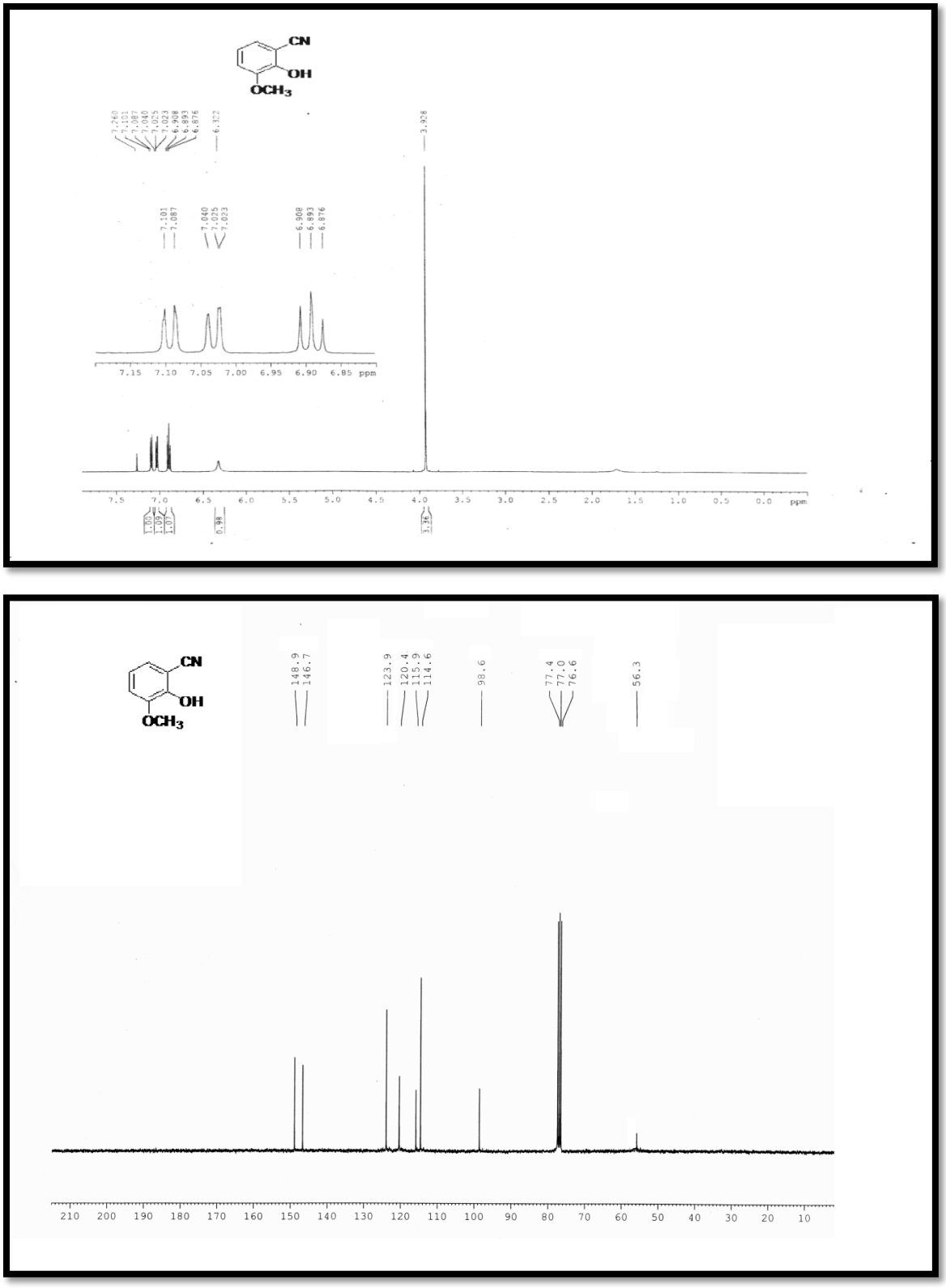
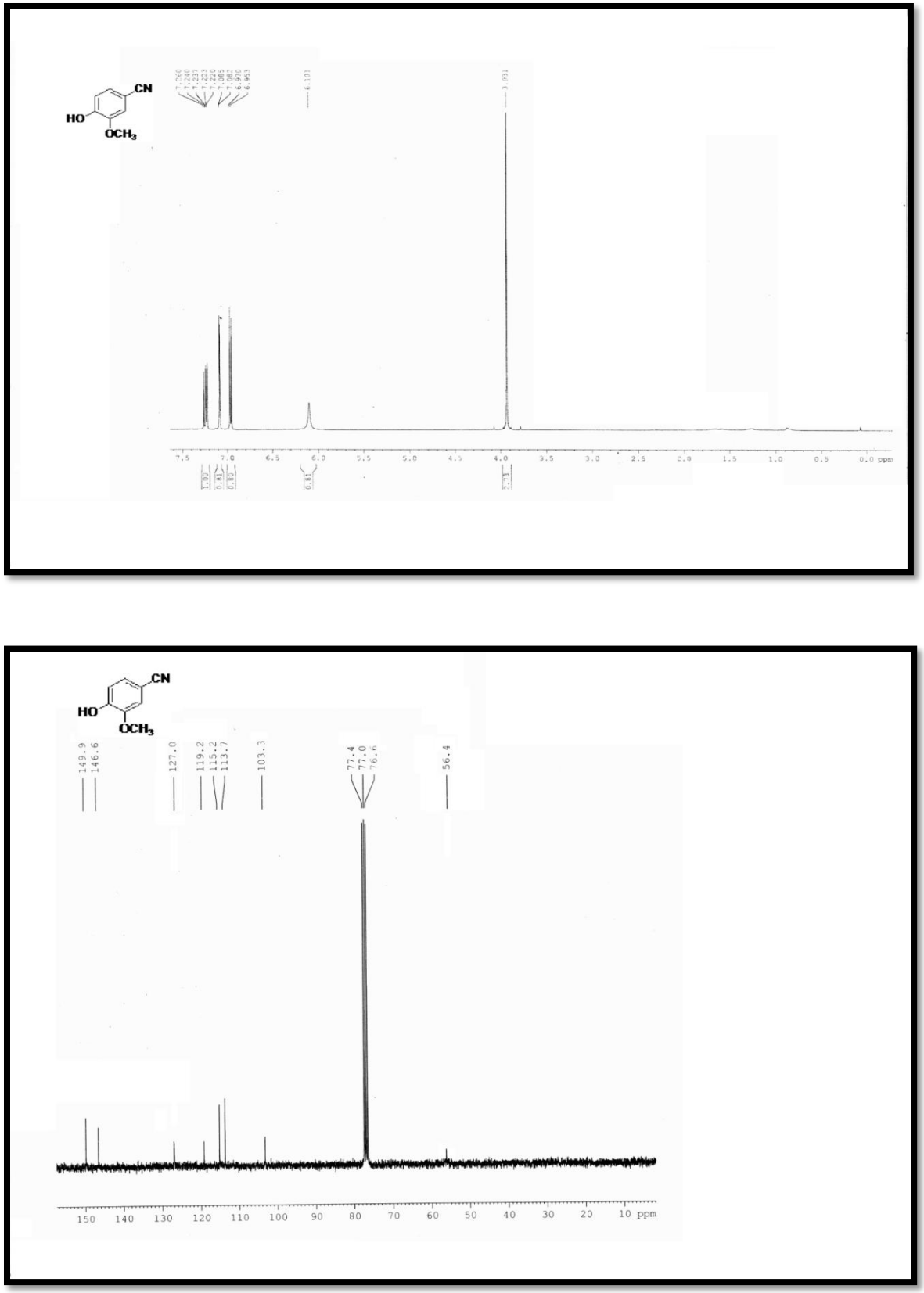


Fig. II. B. 12. : ^{1}H and ^{13}C NMR of 2-Hydroxy-3-methoxy-benzonitrile



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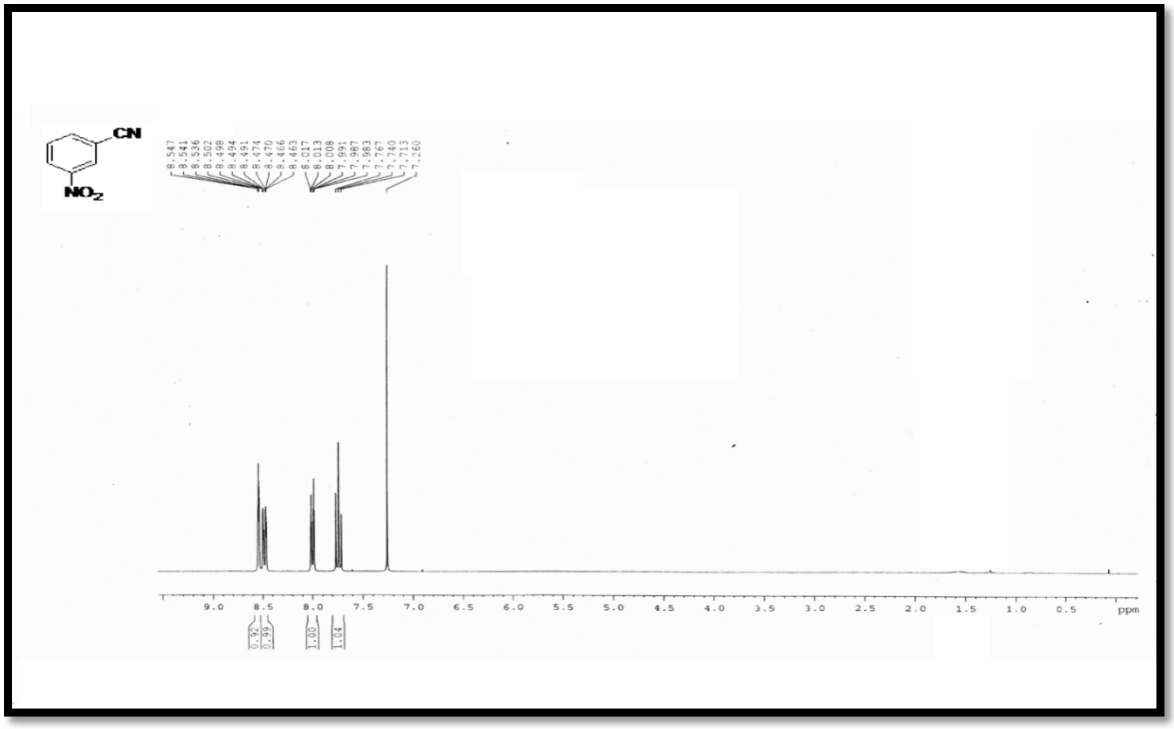

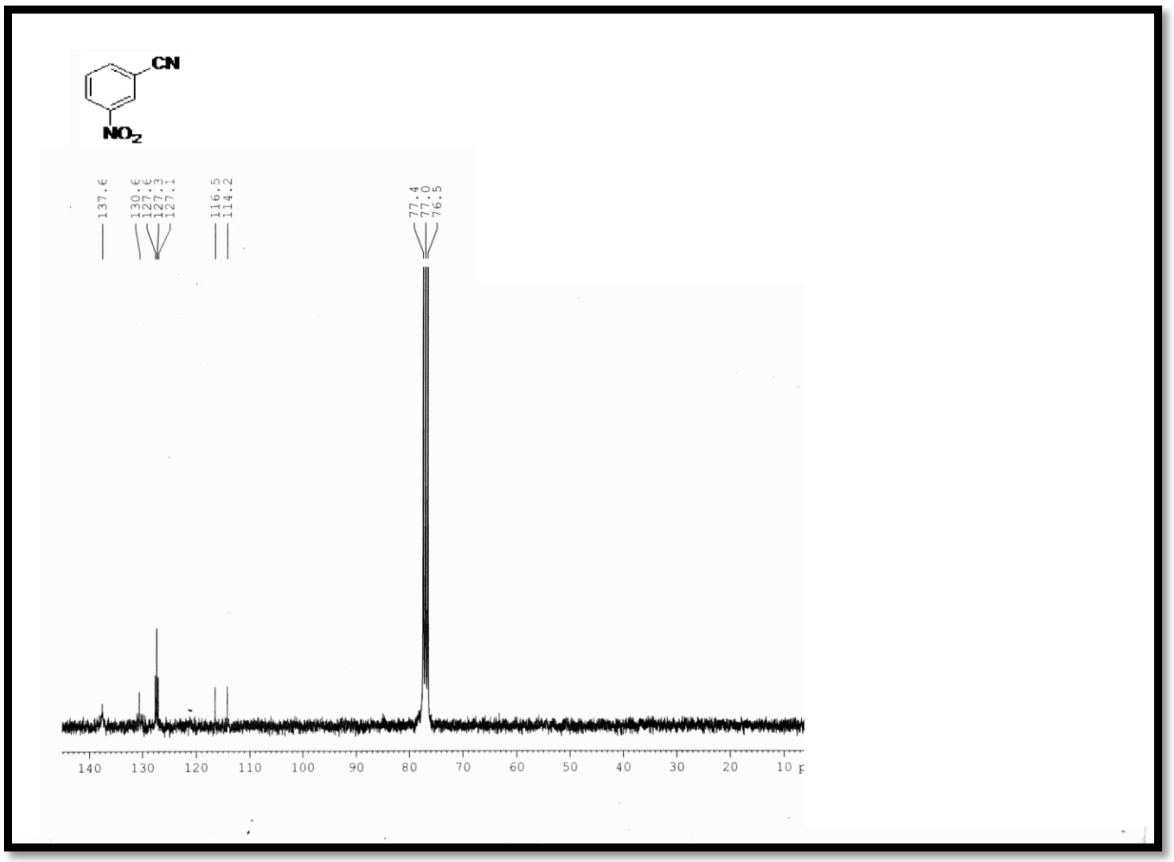

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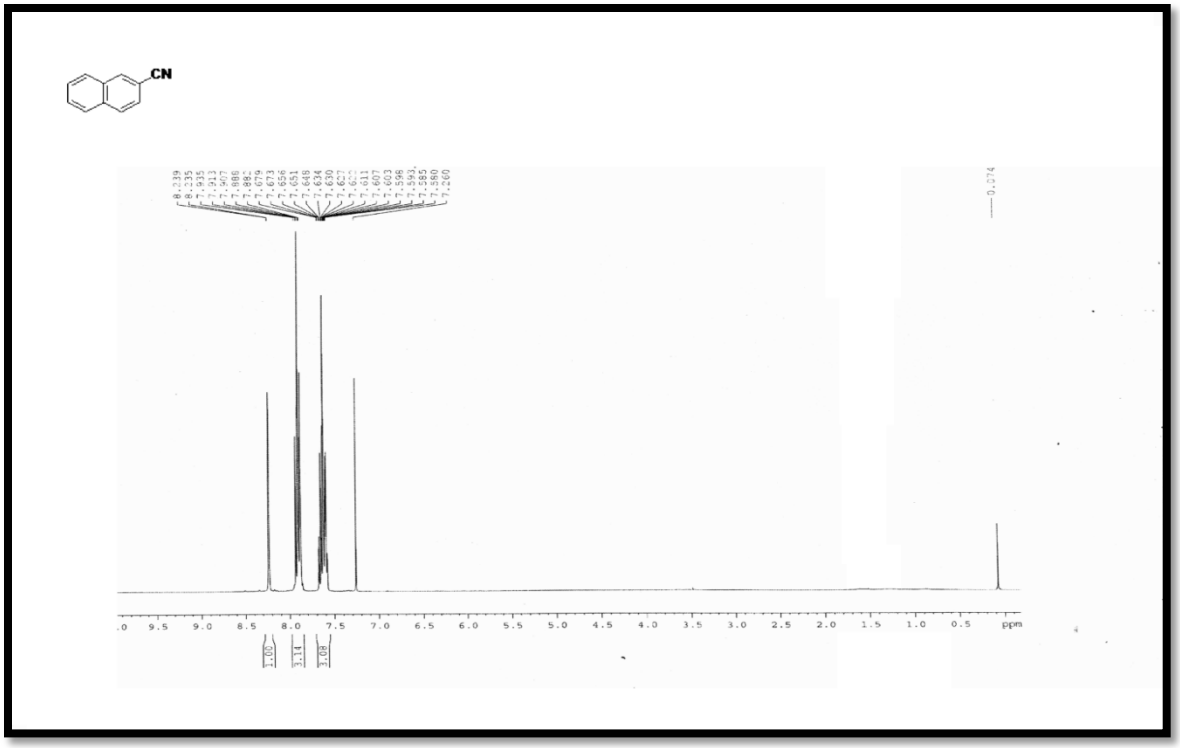


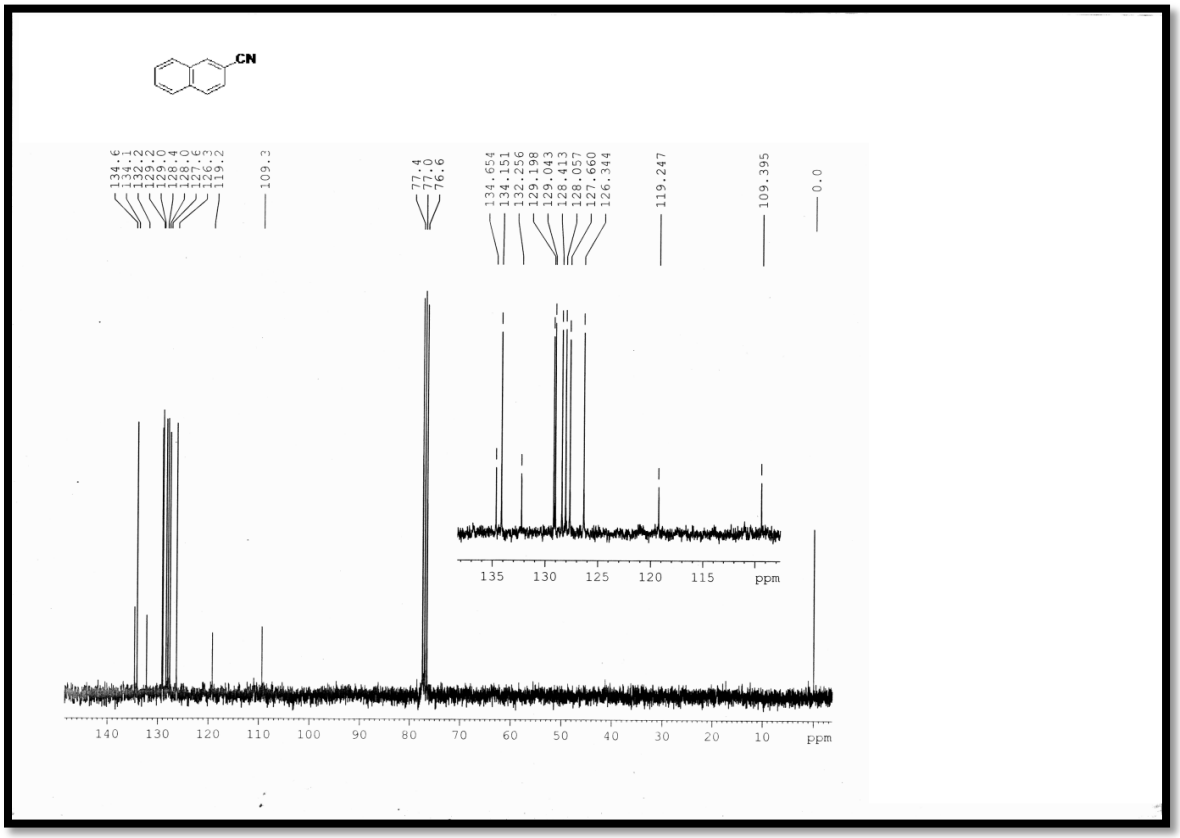
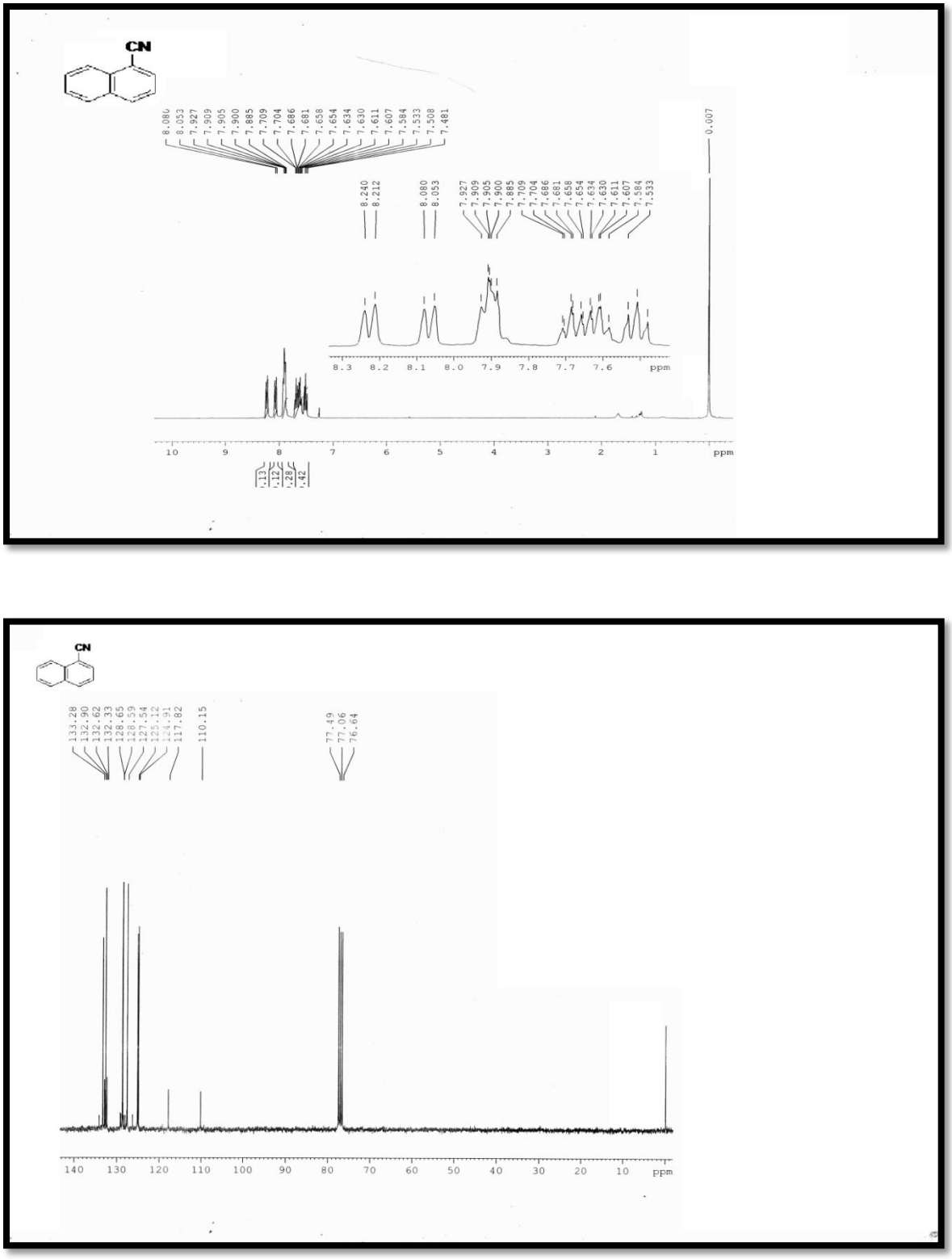


Fig. II. B. 15. : ^{1}H and ^{13}C NMR of Napthalene-2-carbonitrile



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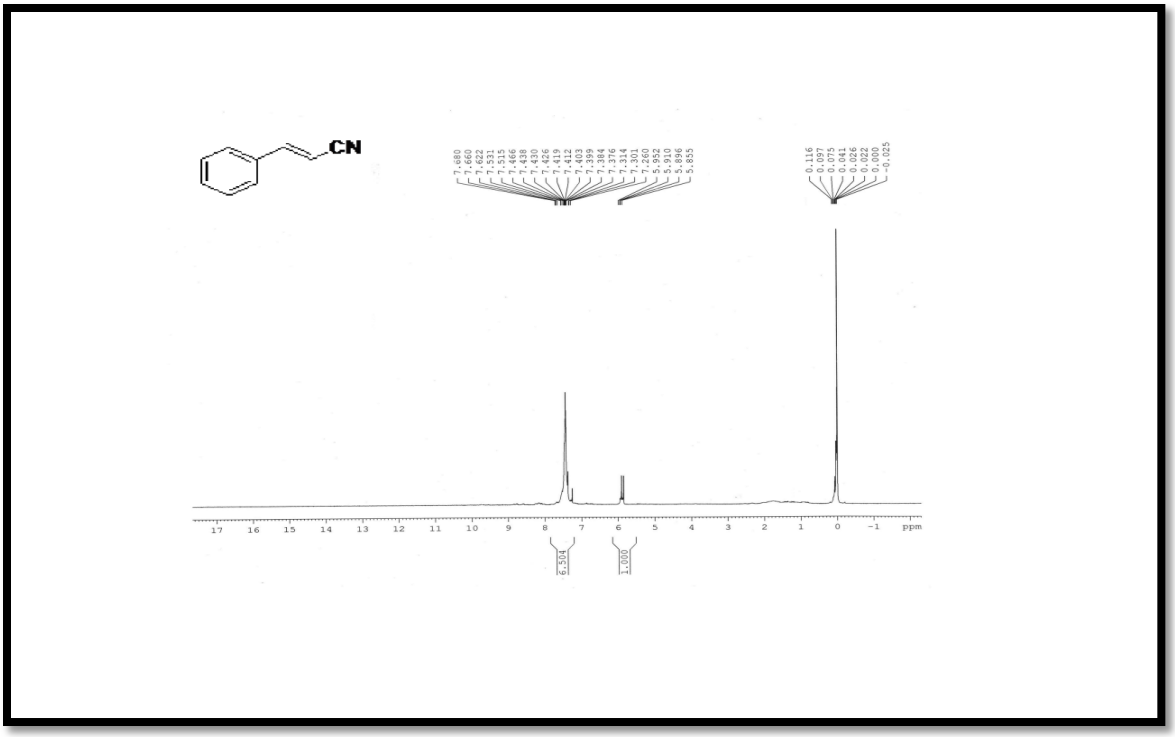

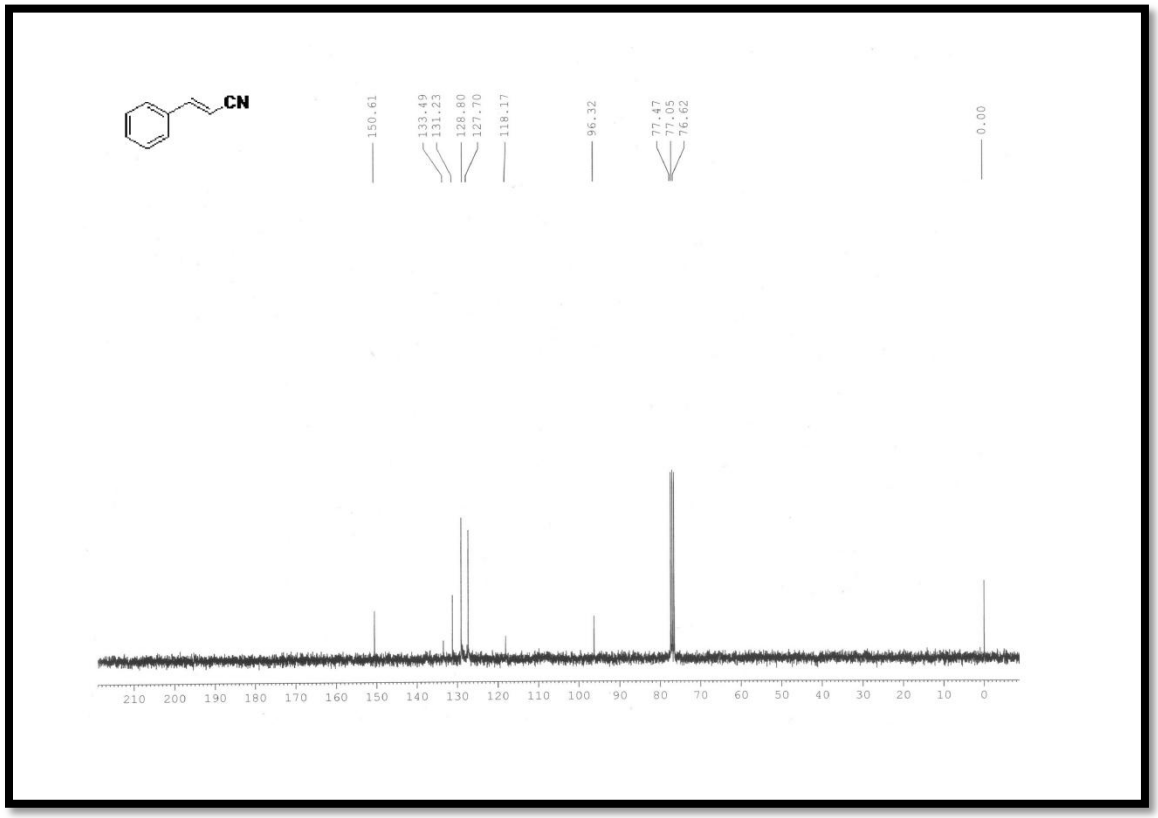

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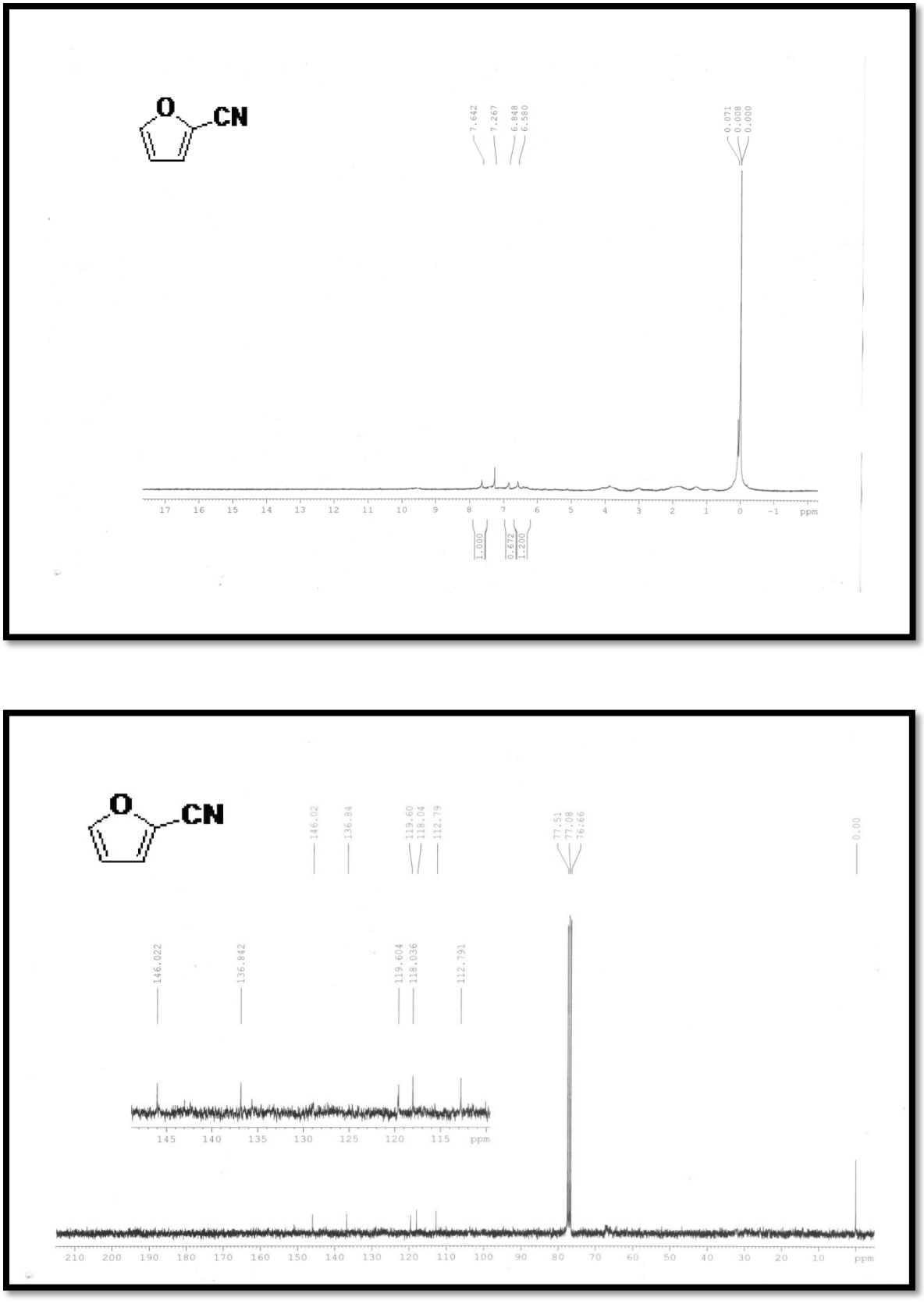

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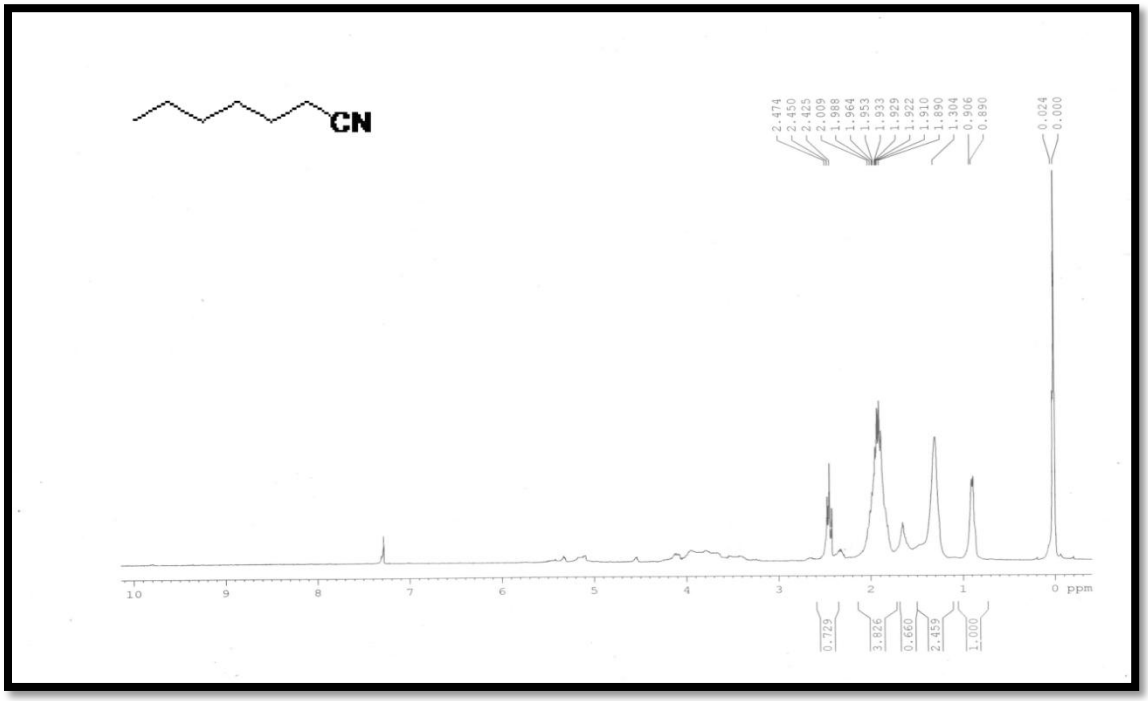

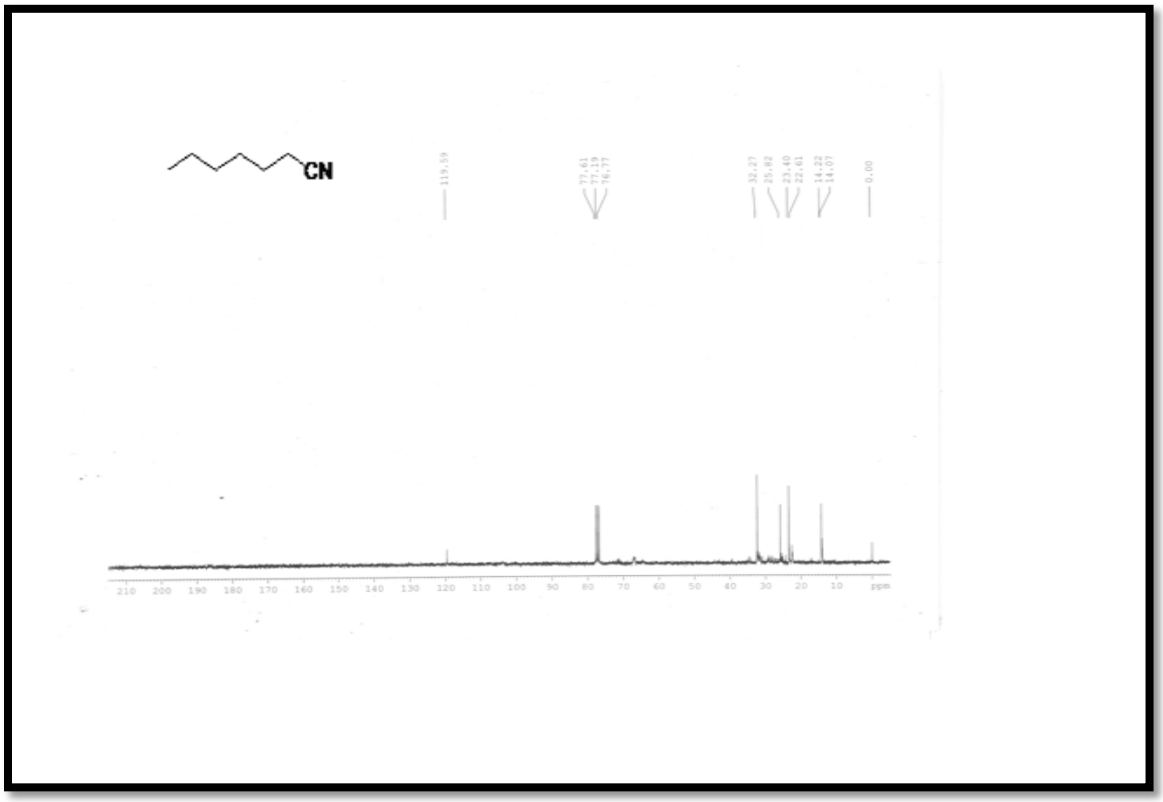

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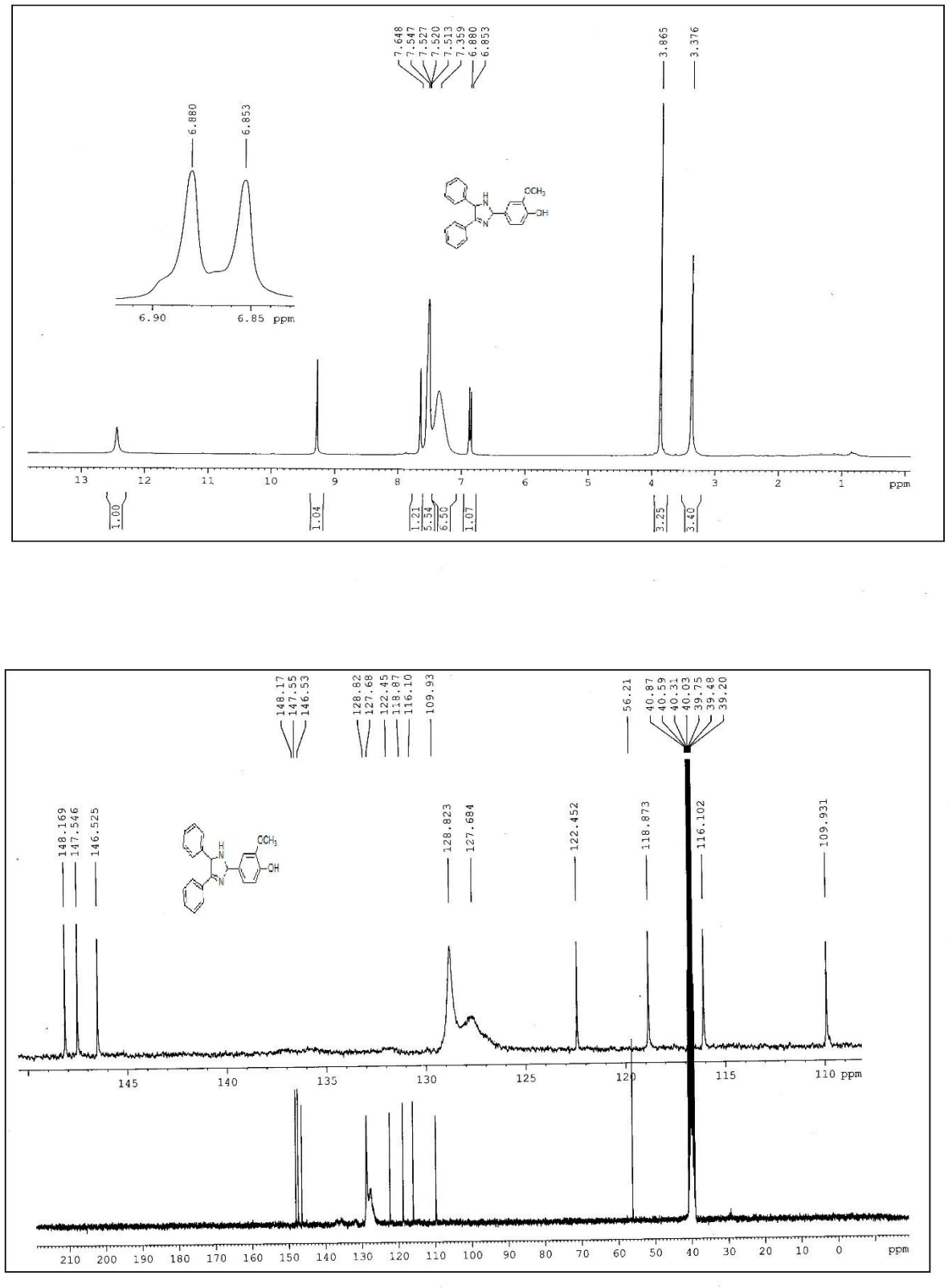


Fig. III. B. 8. ^{1}H and ^{13}C NMR of 2-(4-hydroxy-3-methoxyphenyl)-4, 5-diphenyl-1*H*-imidazole

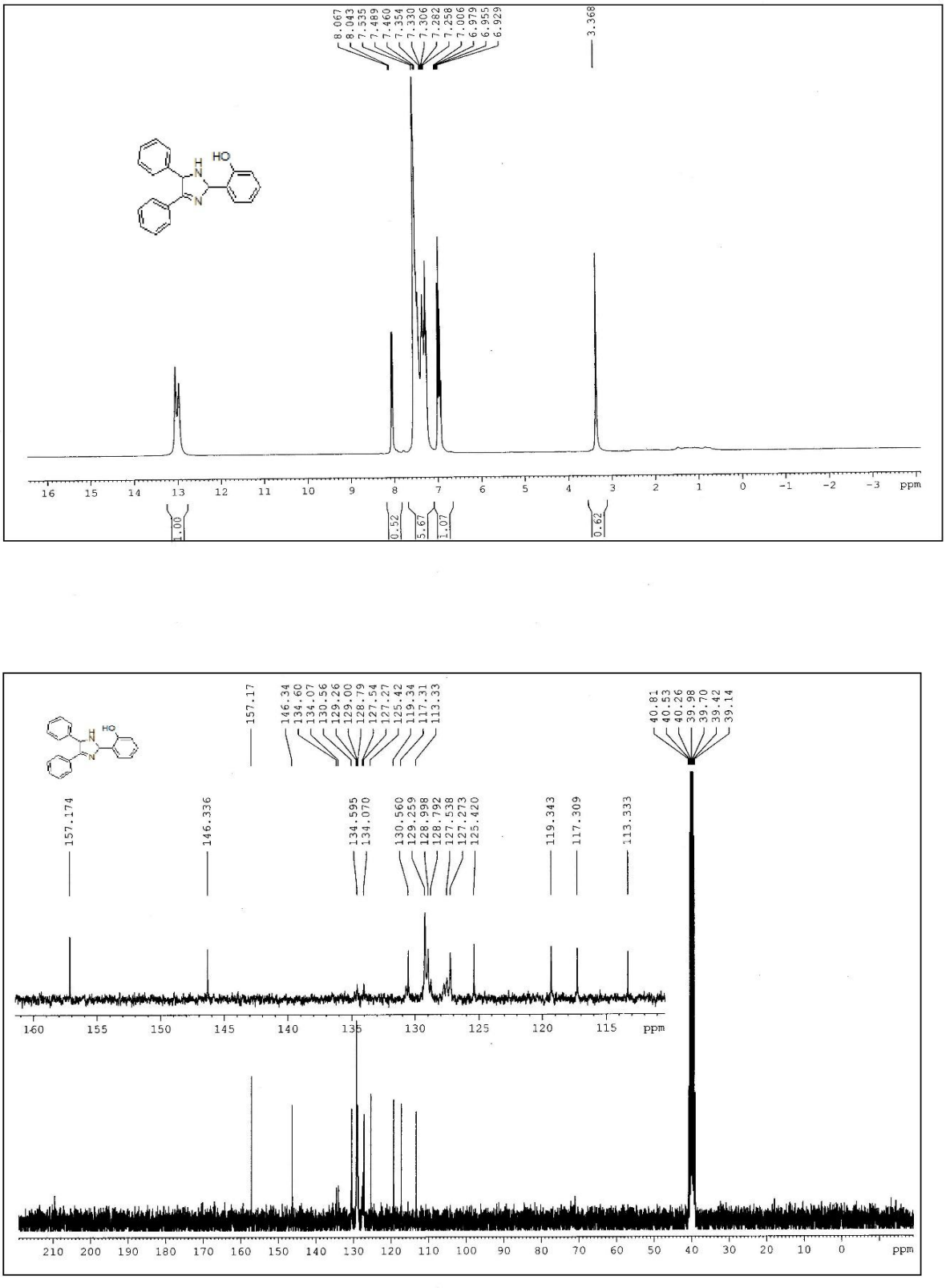


Fig. III. B. 9. ^{1}H and ^{13}C NMR of 2-(2-hydroxyphenyl)-4, 5-diphenyl-1*H*-imidazole

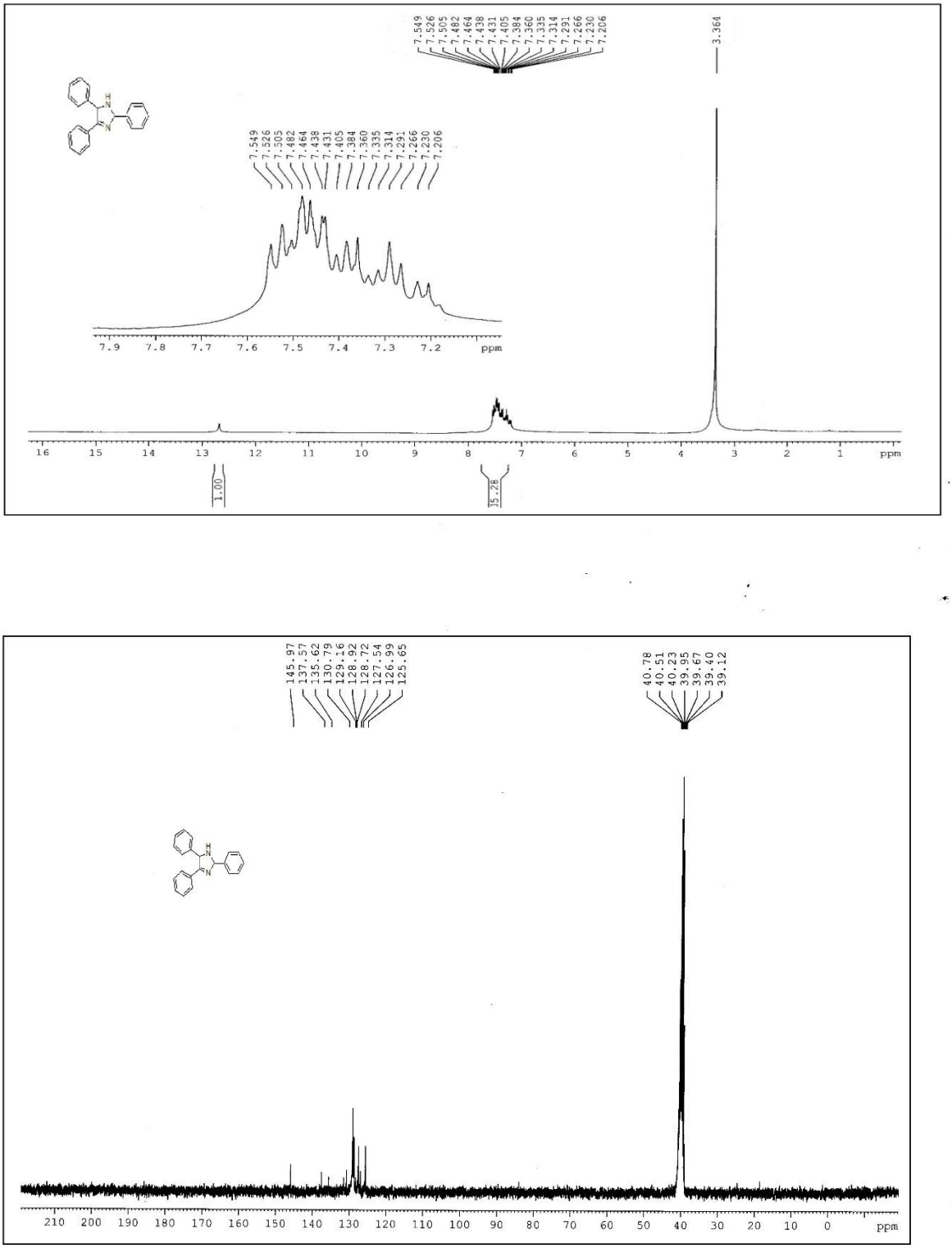
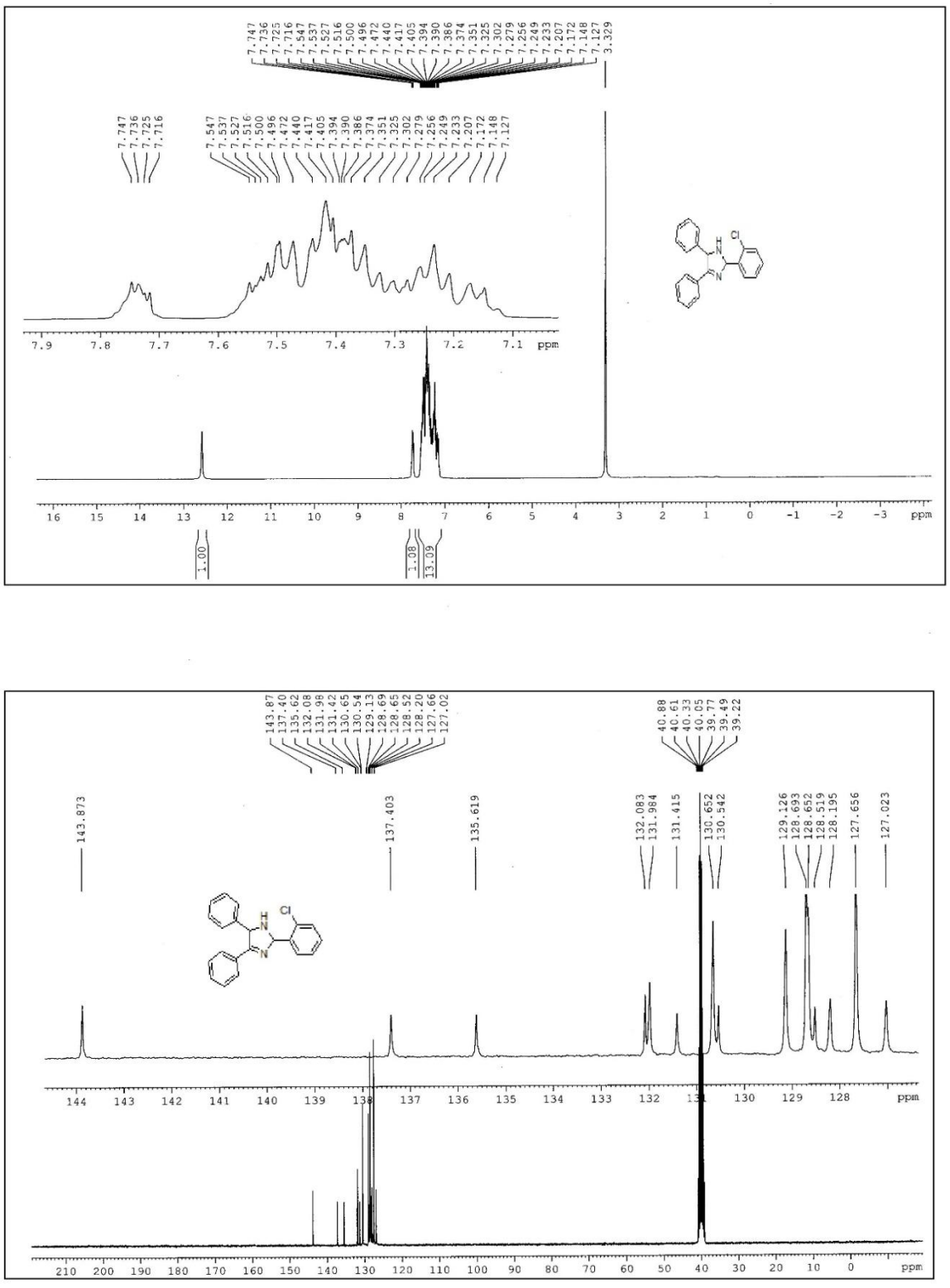


Fig. III. B. 10. ^{1}H and ^{13}C NMR of 2, 4, 5-triphenyl-1*H*-imidazole



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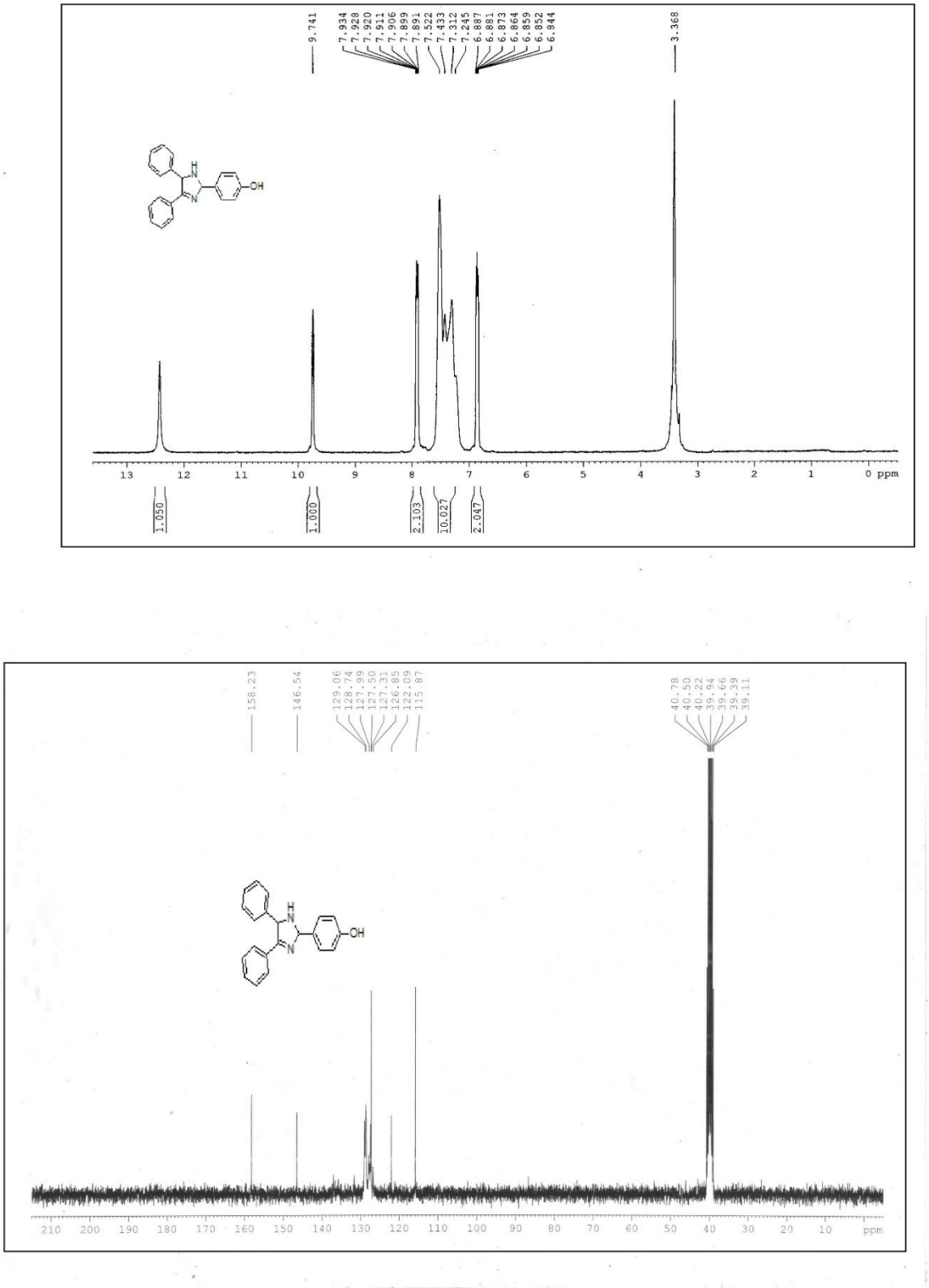

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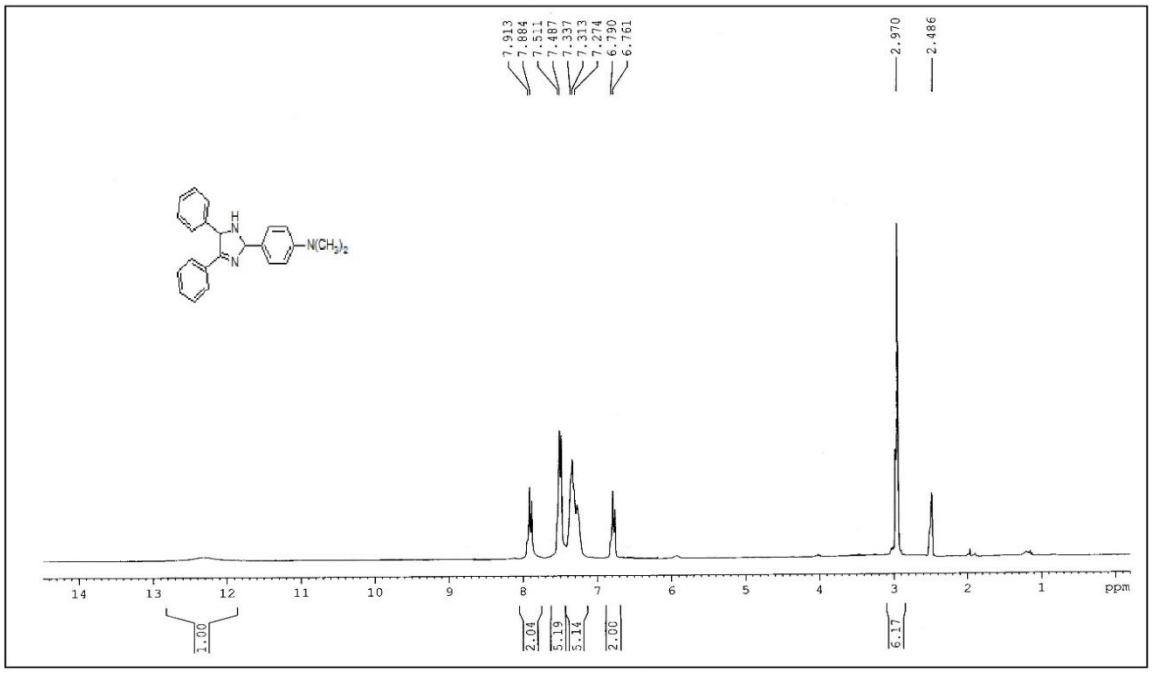

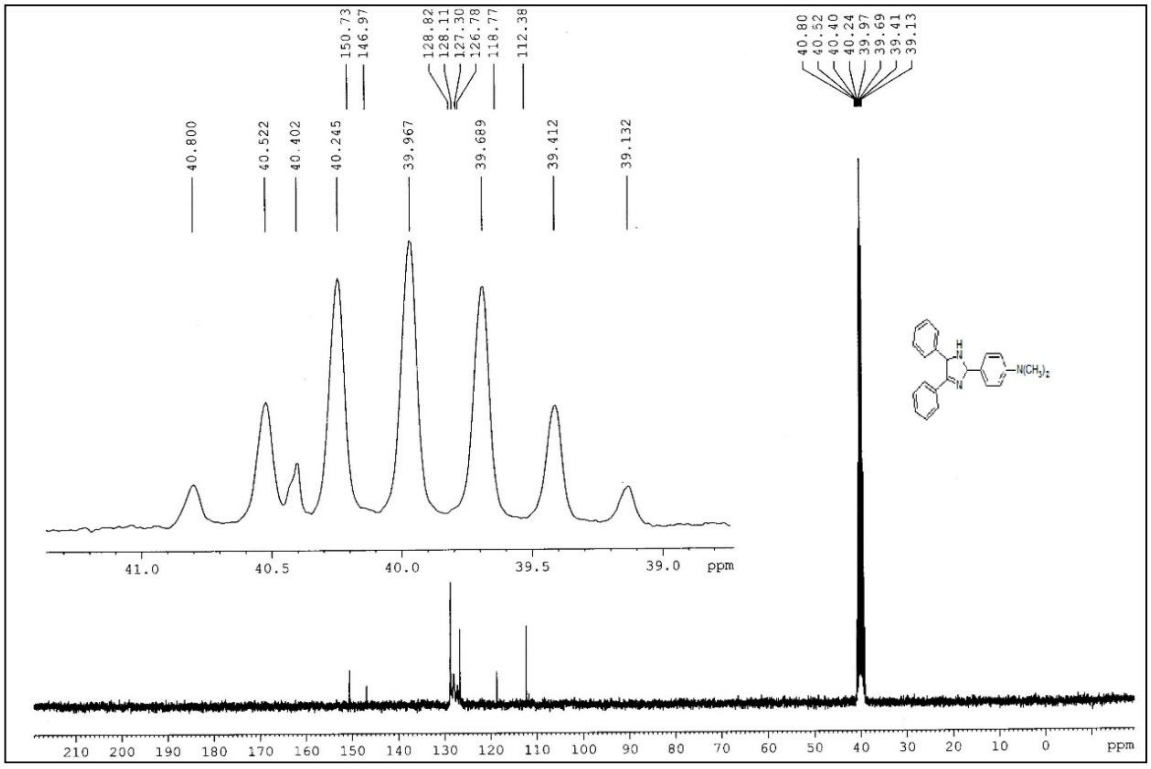

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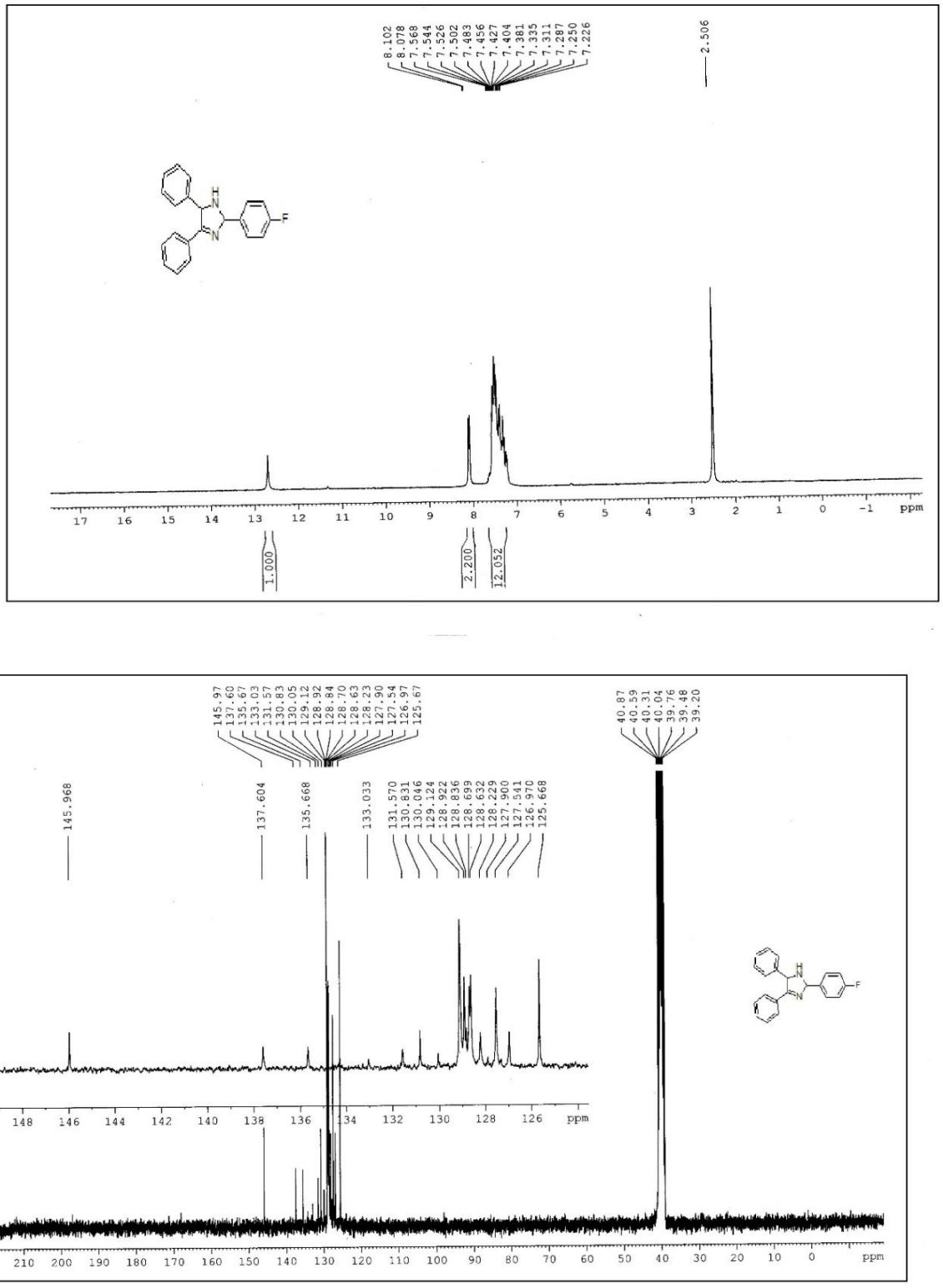


Fig. III. B. 14. ^{1}H and ^{13}C NMR of 2-(4-fluorophenyl)-4, 5-diphenyl-1*H*-imidazole

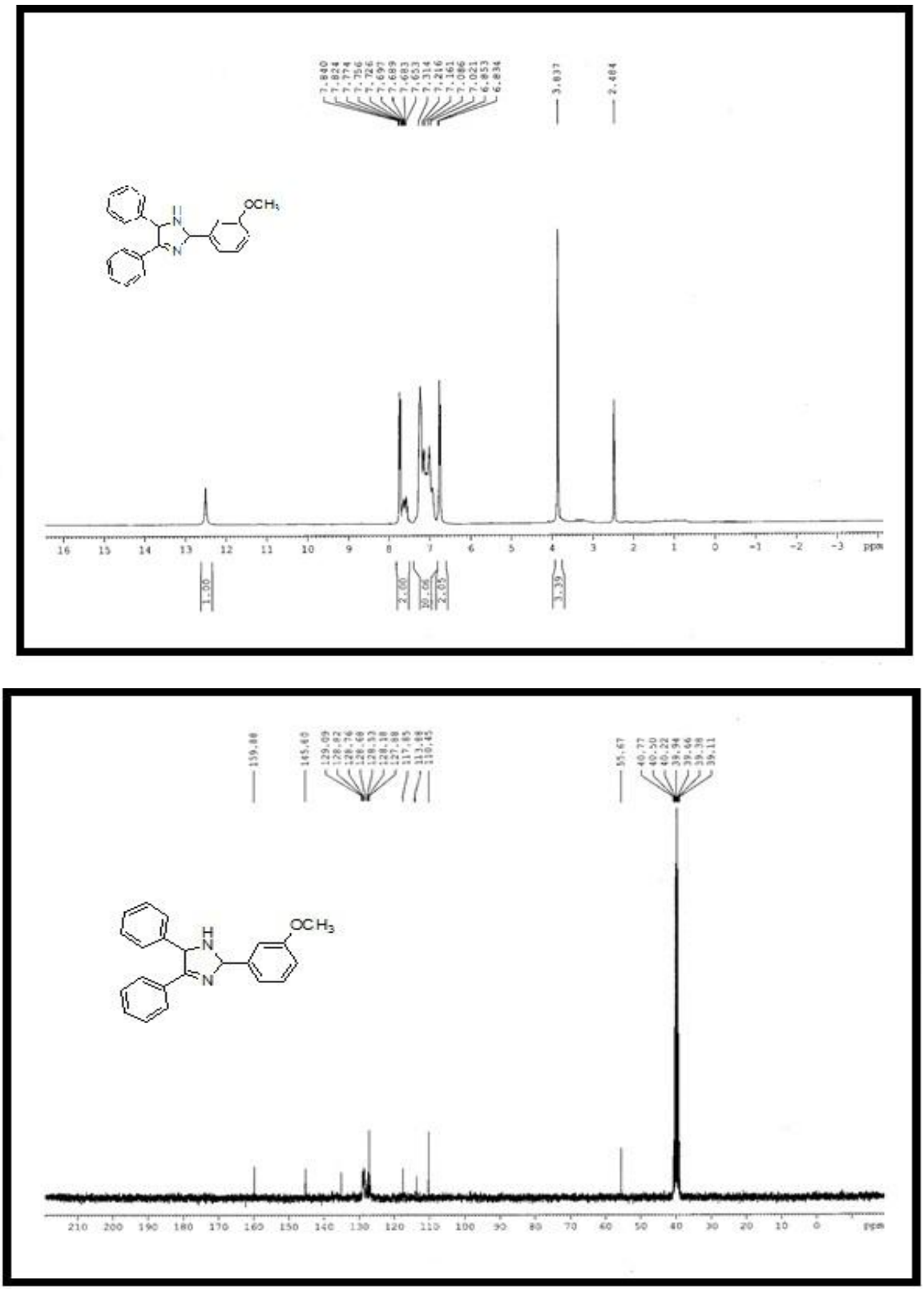
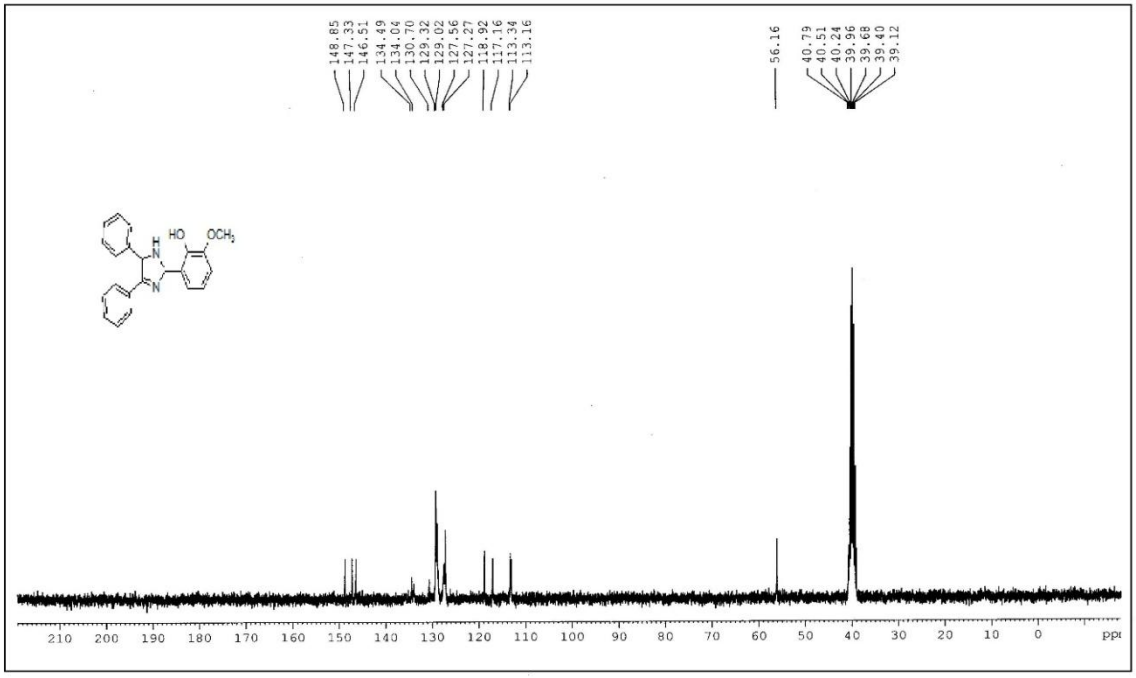


Fig. III. B. 15. ^{1}H and ^{13}C NMR of 2-(4-methoxypyridine-2-yl)-4, 5-diphenyl-1*H*-imidazole



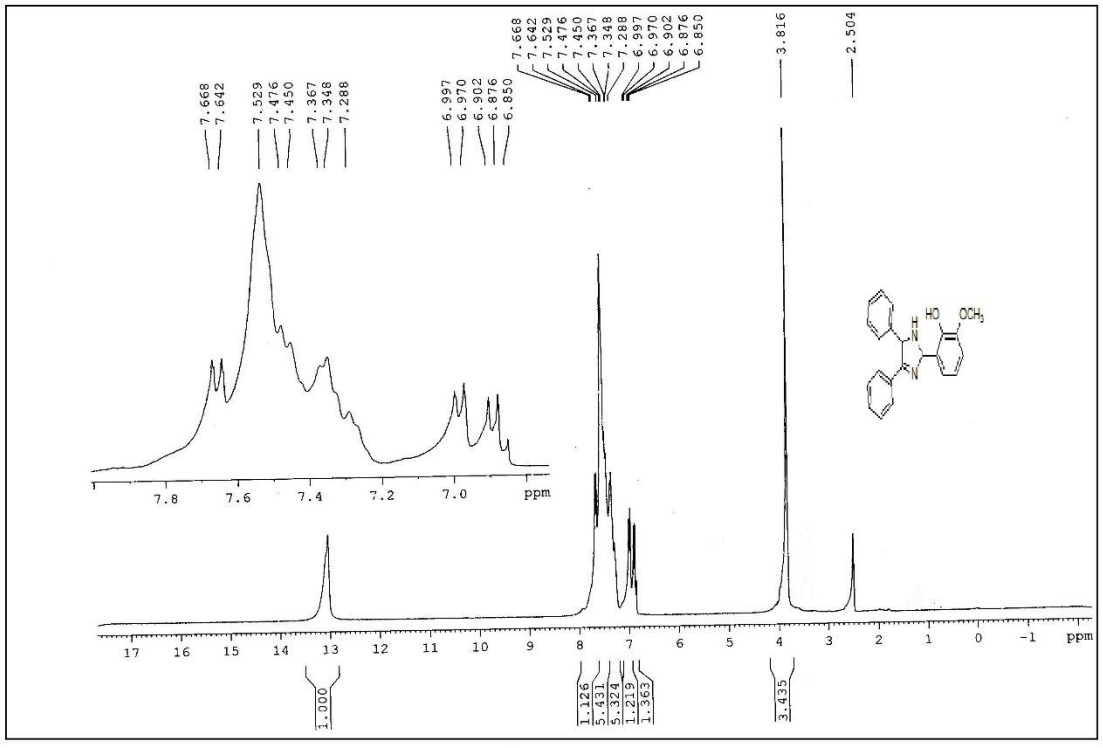


Fig. III. B. 16. ^{1}H and ^{13}C NMR of 2-(2-hydroxy-3-methoxyphenyl)-4, 5-diphenyl-1*H*-imidazole

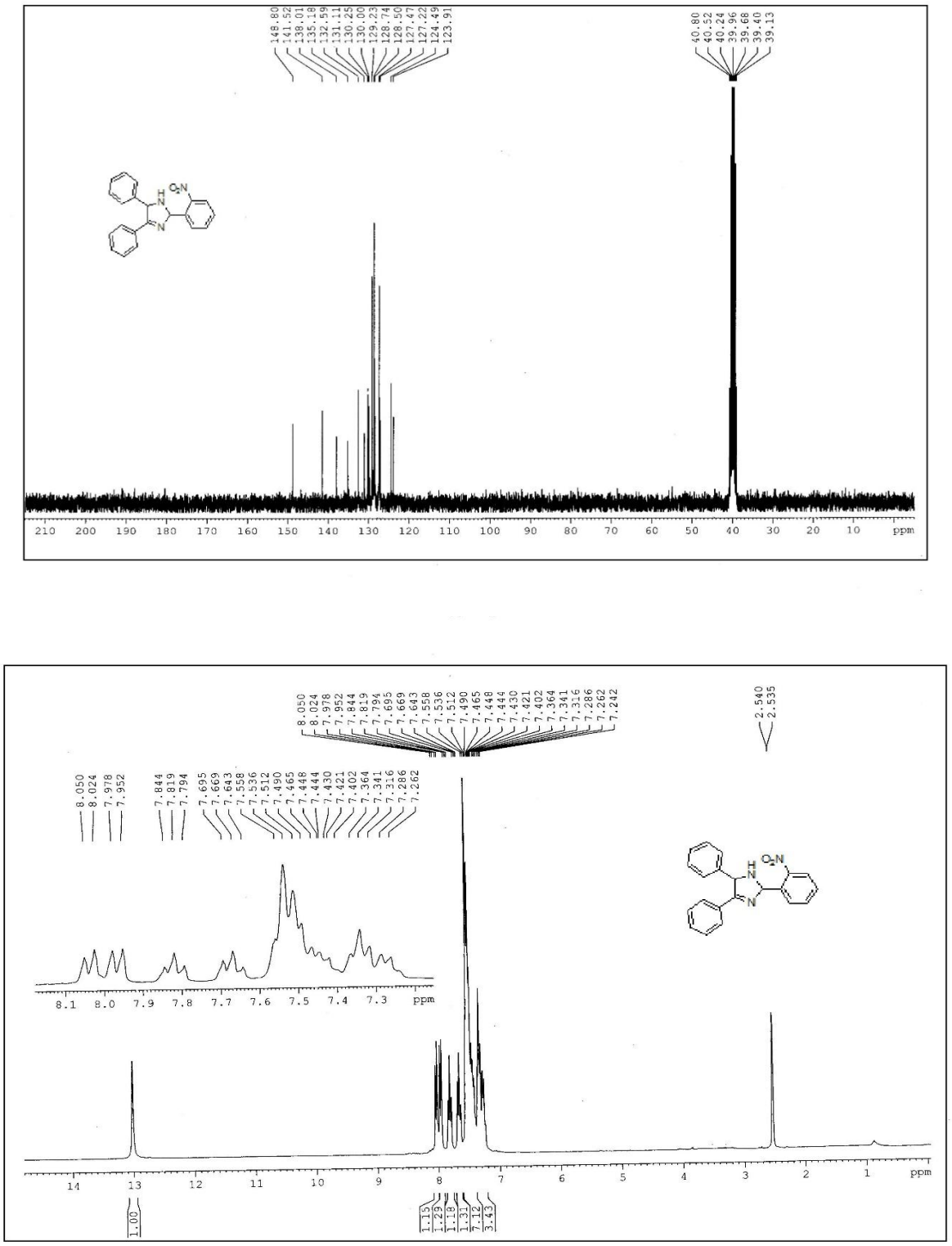
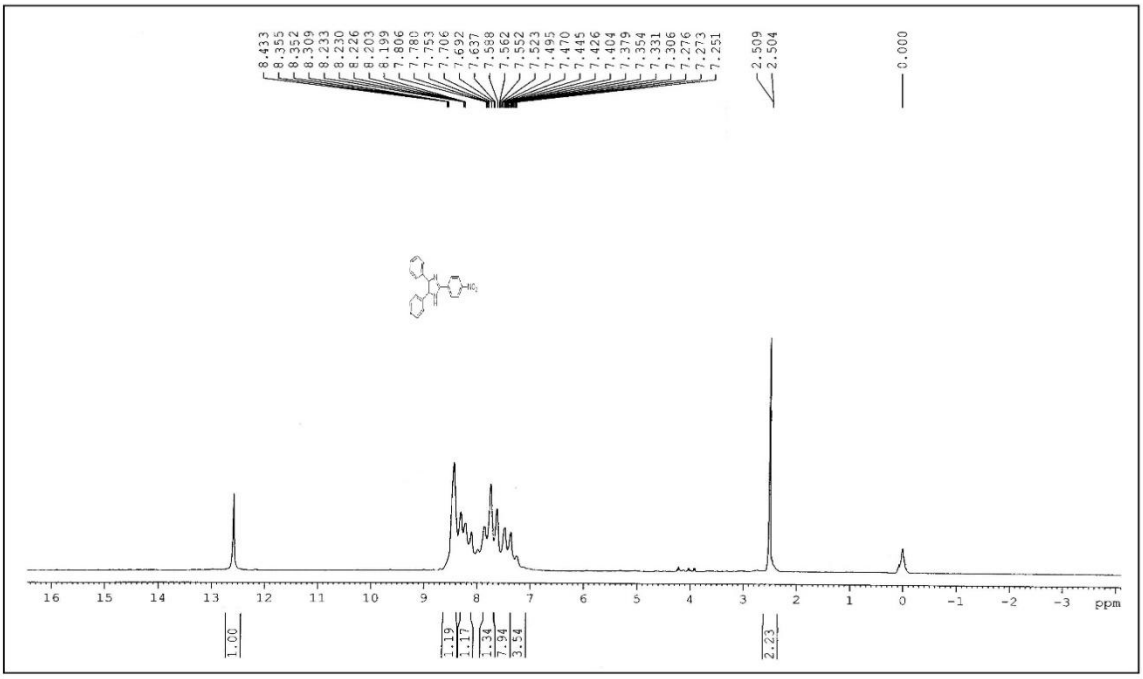


Fig. III. B. 17. ^{1}H and ^{13}C NMR of 2-(2-nitrophenyl)-4, 5-diphenyl-1*H*-imidazole



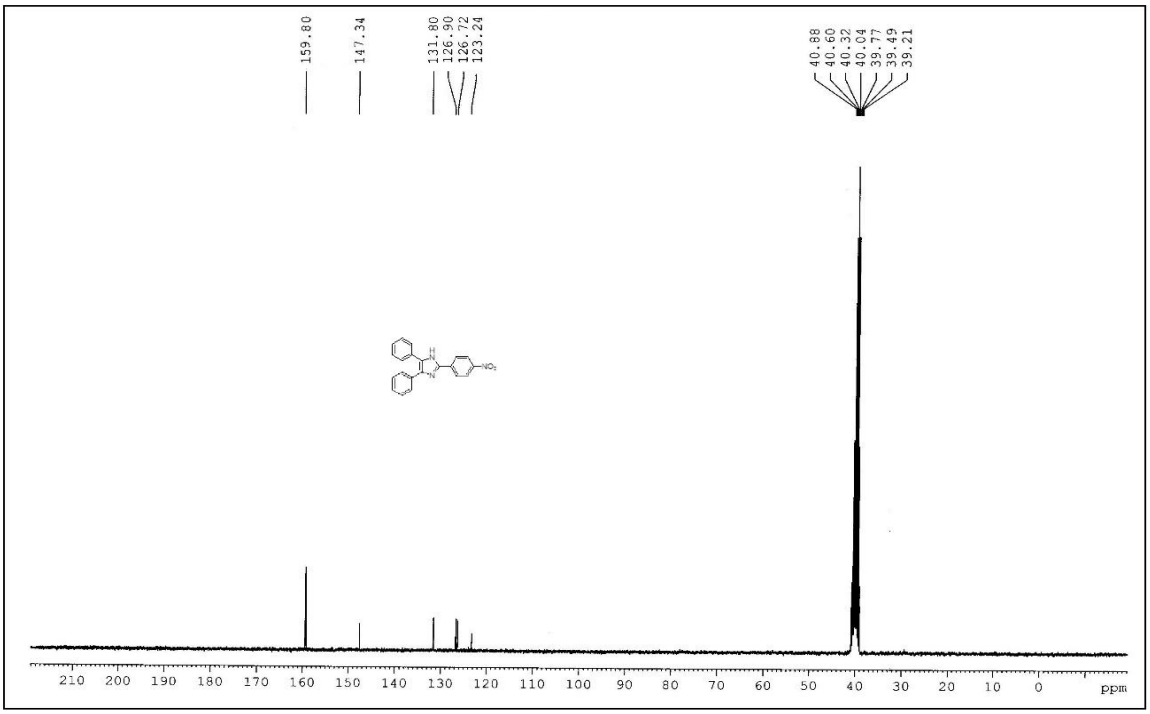


Fig. III. B. 18. ^{1}H and ^{13}C NMR of 2-(4-Nitrophenyl)-4, 5-diphenyl-1*H*-imidazole

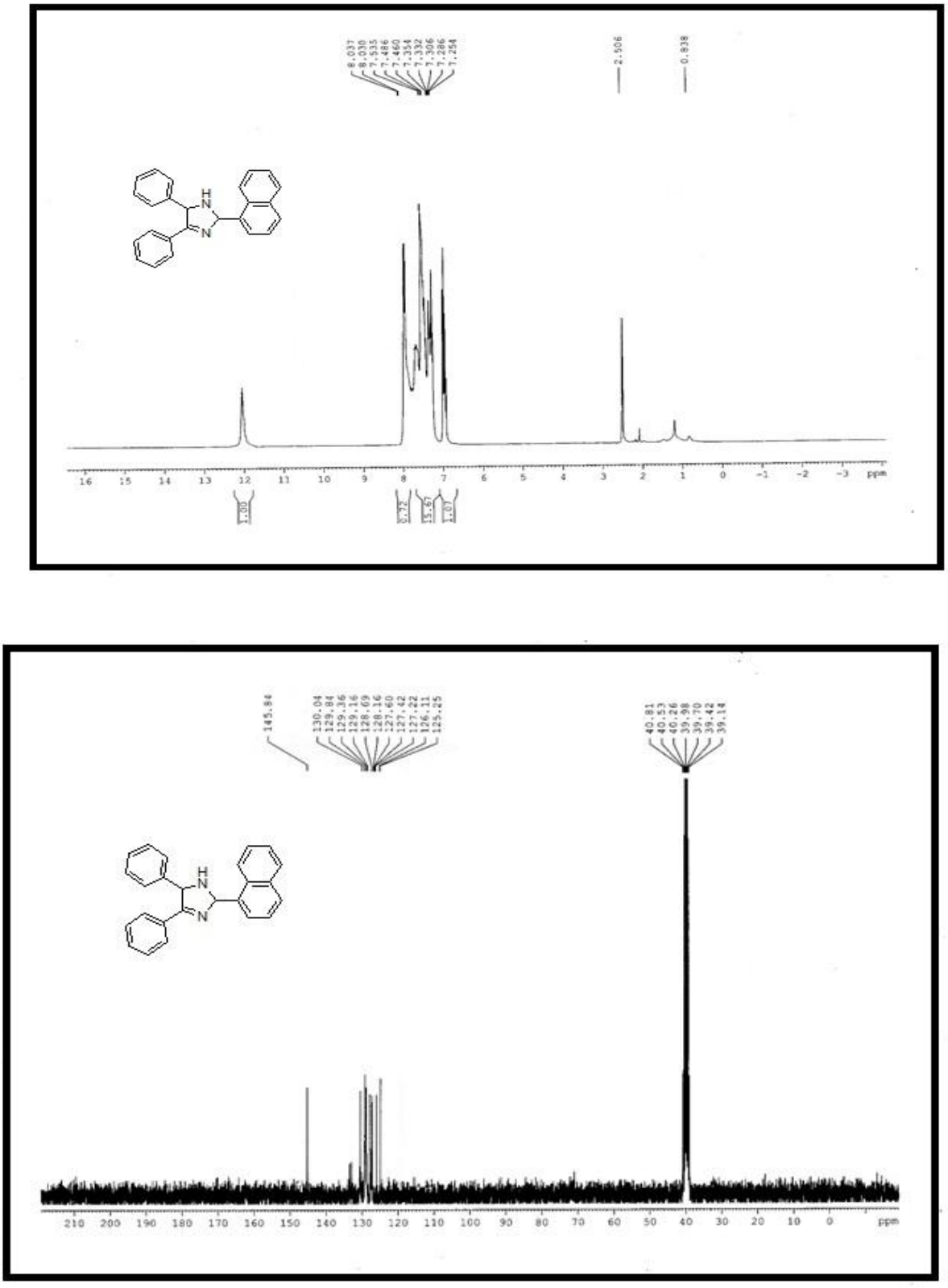
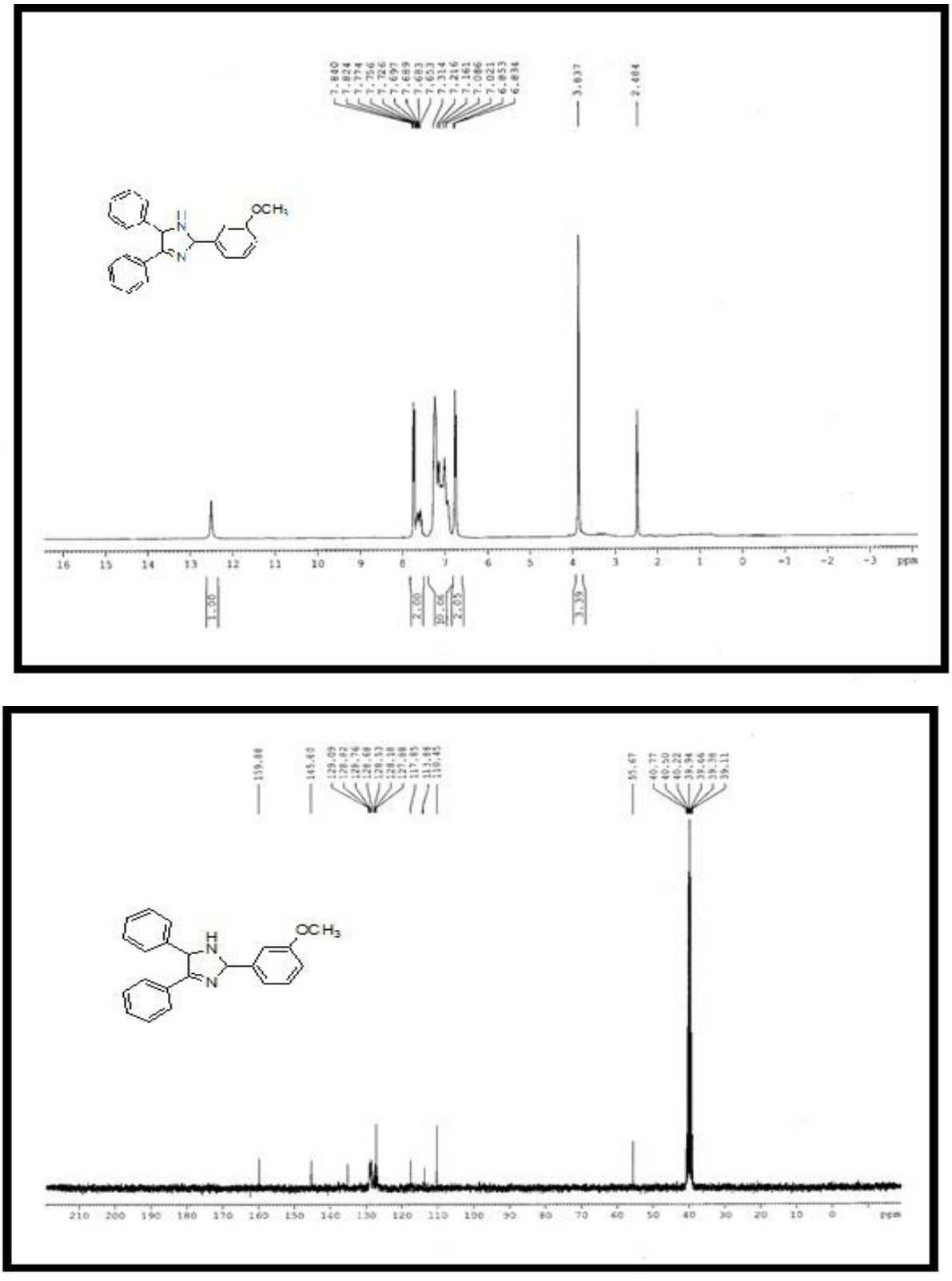


Fig. III. B. 19. ^{1}H and ^{13}C NMR of 2-(2-Napthyl)-4, 5-diphenyl-1*H*-imidazole



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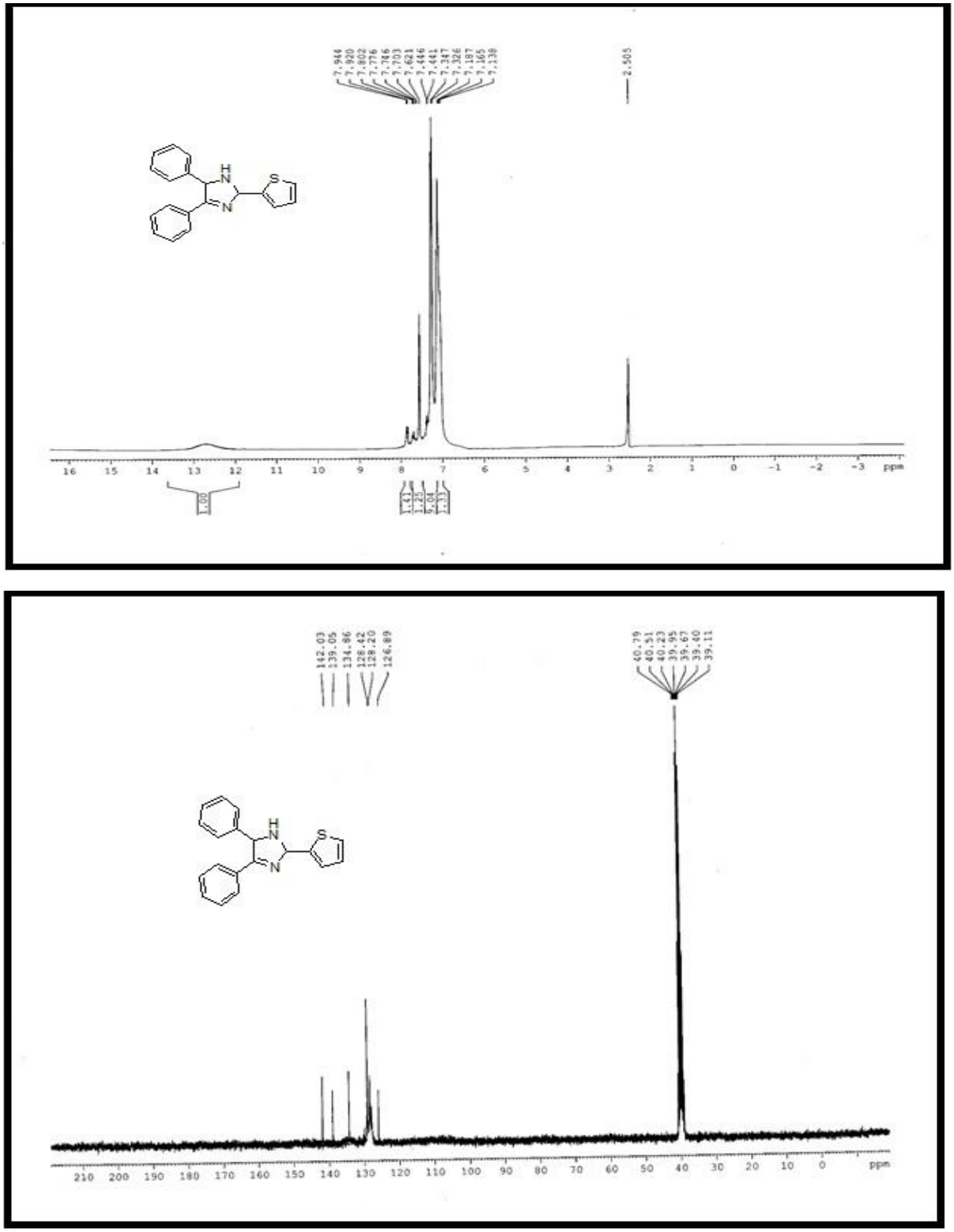


Fig. III. B. 21. ^{1}H and ^{13}C NMR of 4, 5-Diphenyl-2-(thiophen-2-yl)-1*H*-imidazole

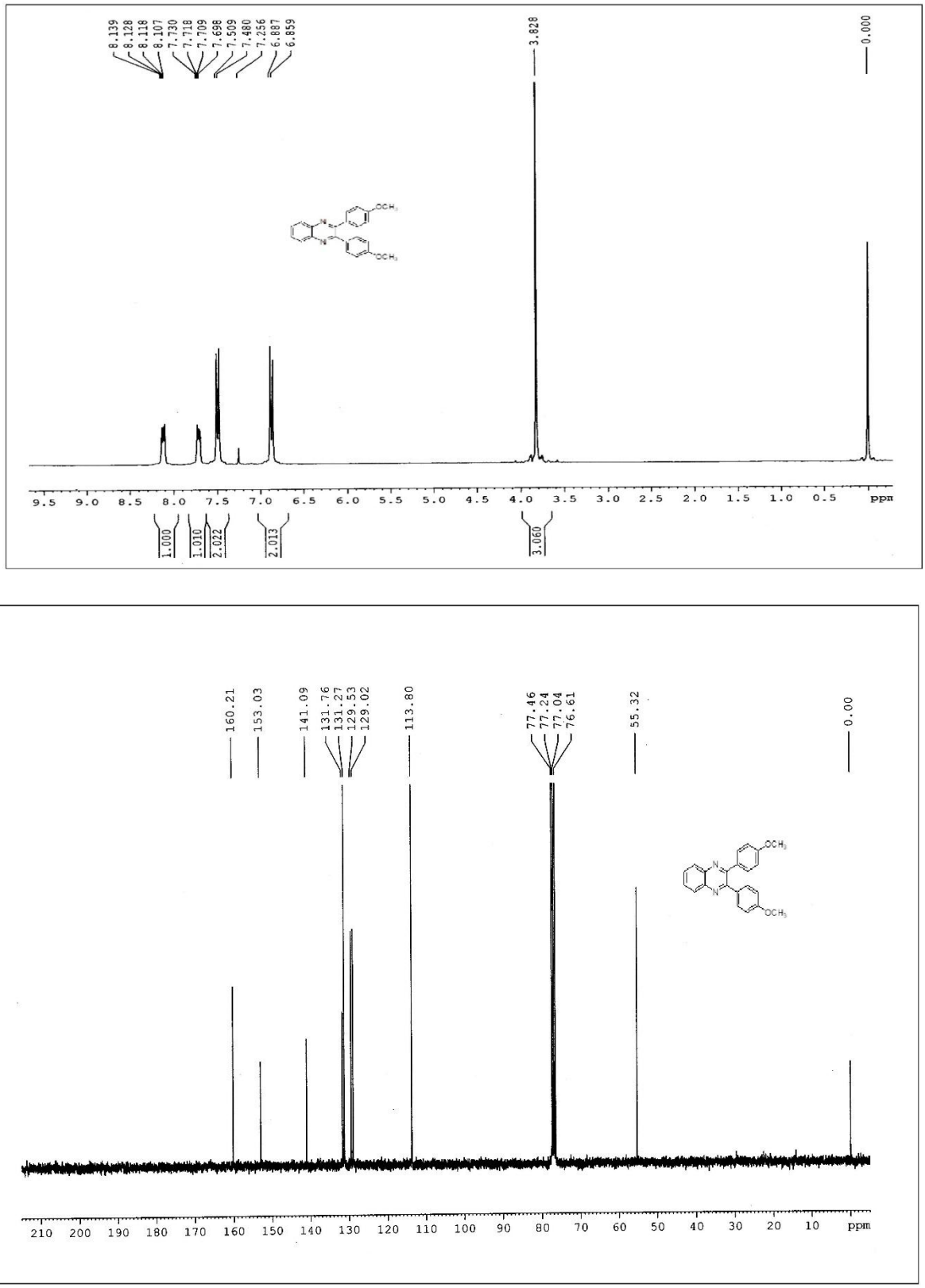
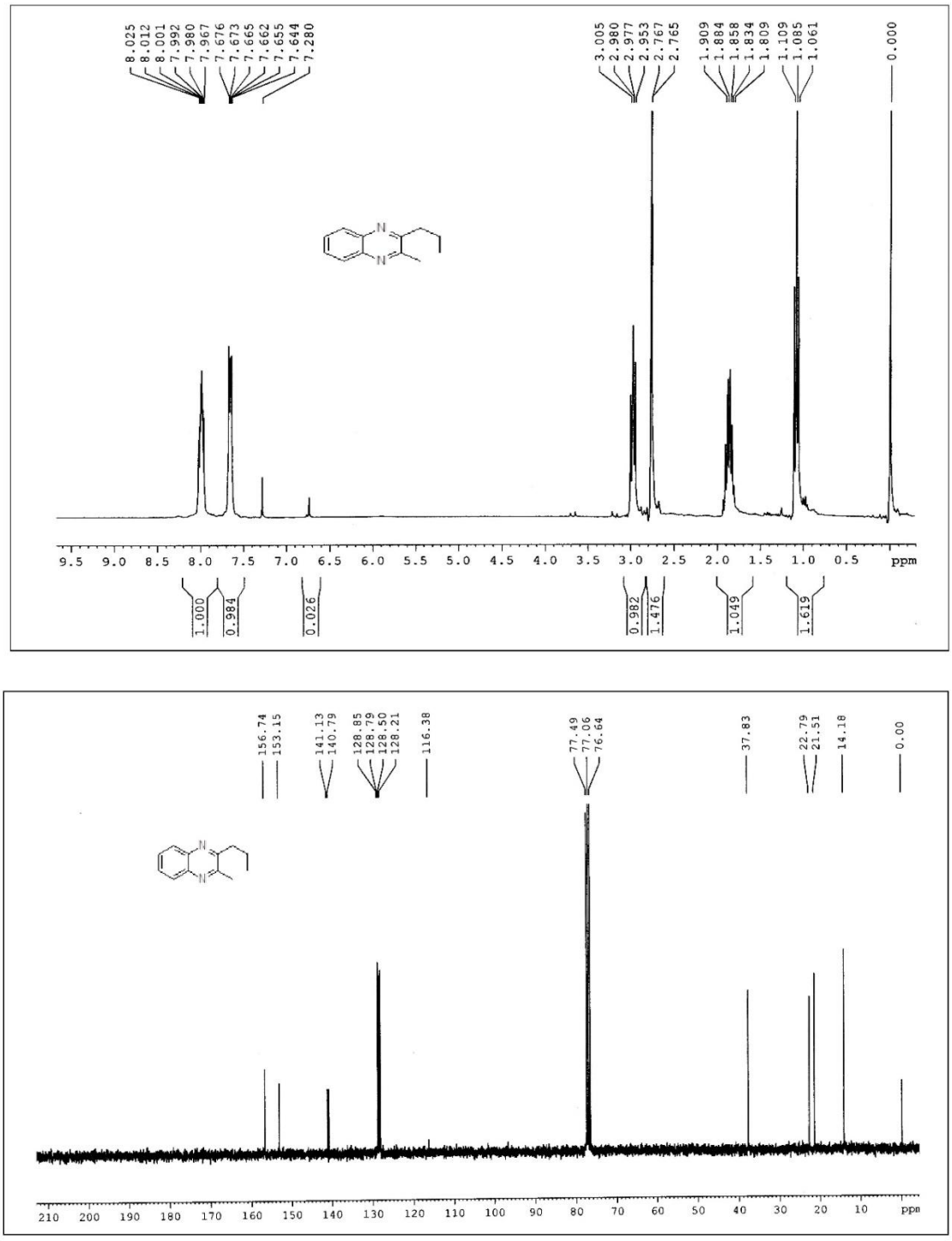


Fig. IV. B. 8. ^{1}H and ^{13}C NMR spectra of 2, 3-Bis (4-methoxyphenyl) quinoxaline



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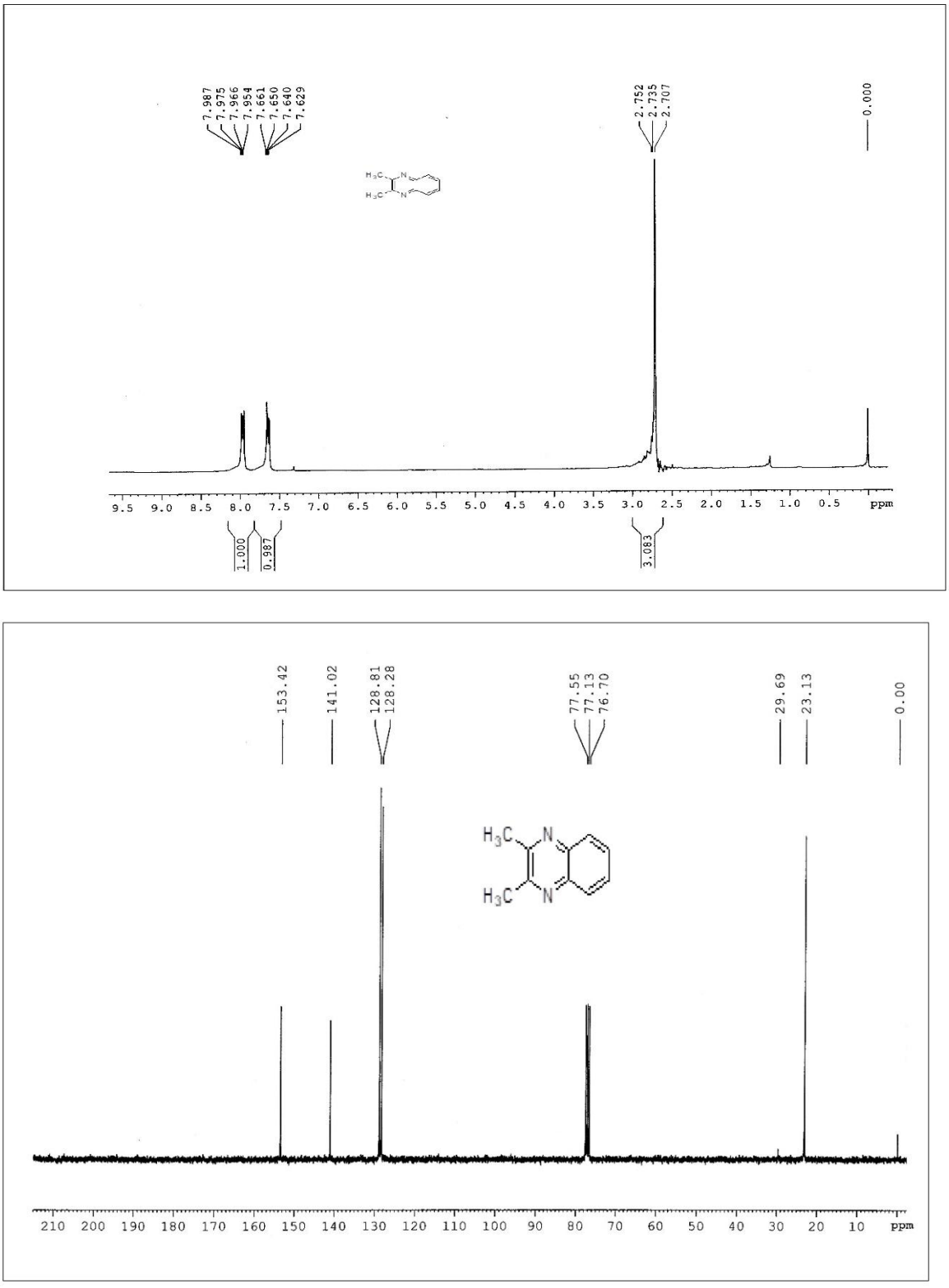
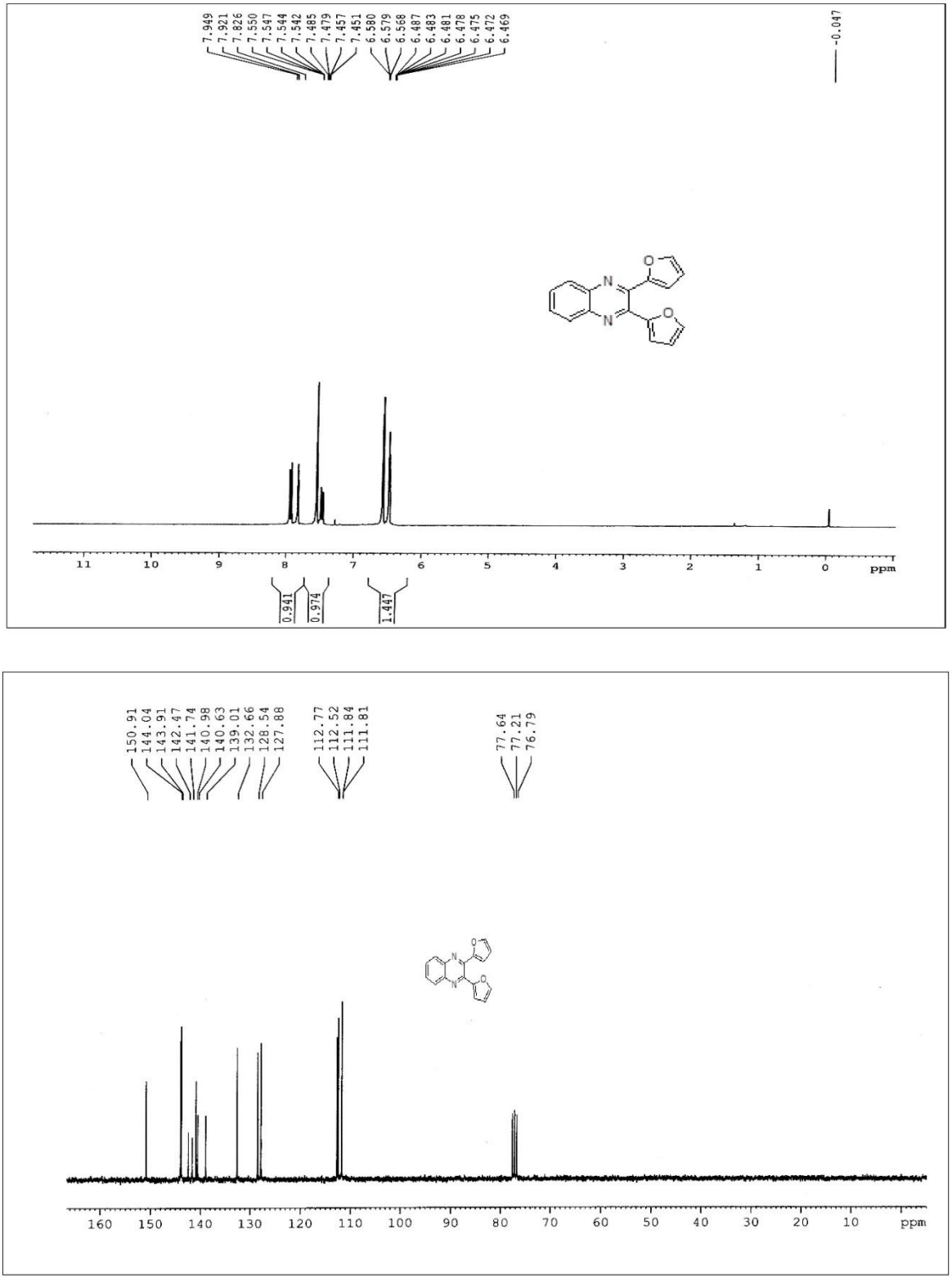


Fig. IV. B. 10. ^{1}H and ^{13}C NMR spectra of 2, 3-Dimethylquinoxaline



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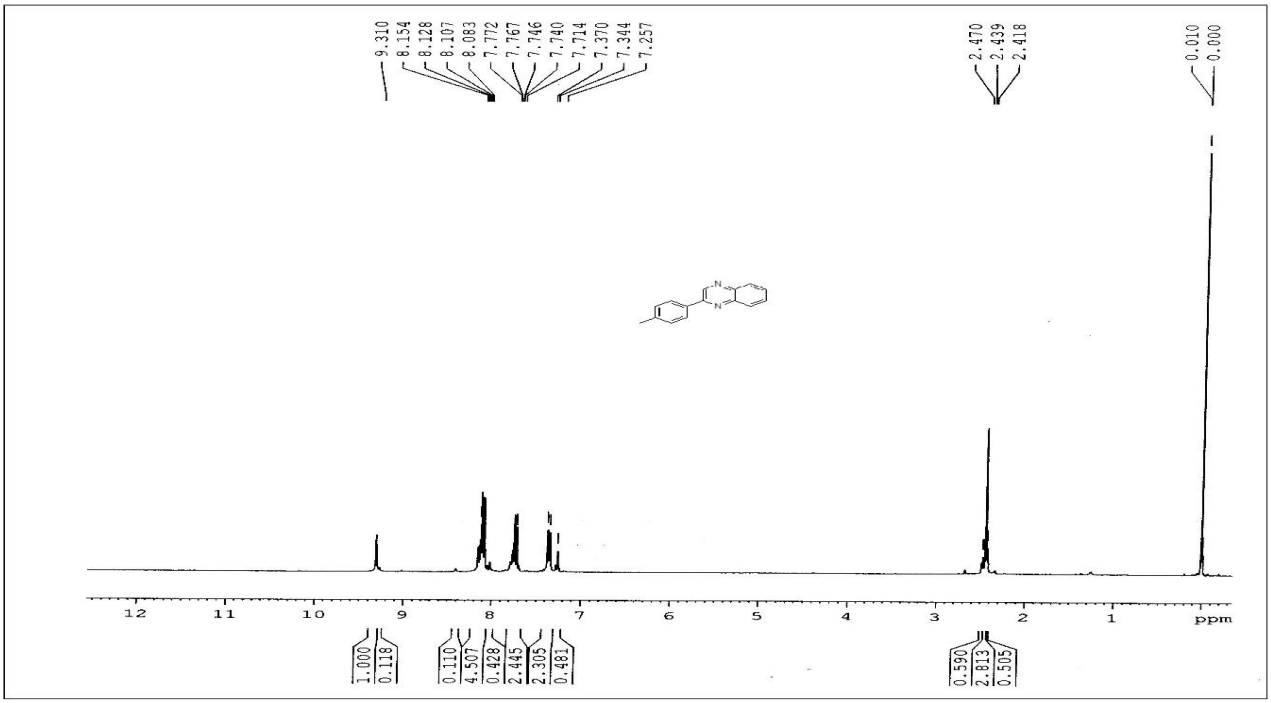


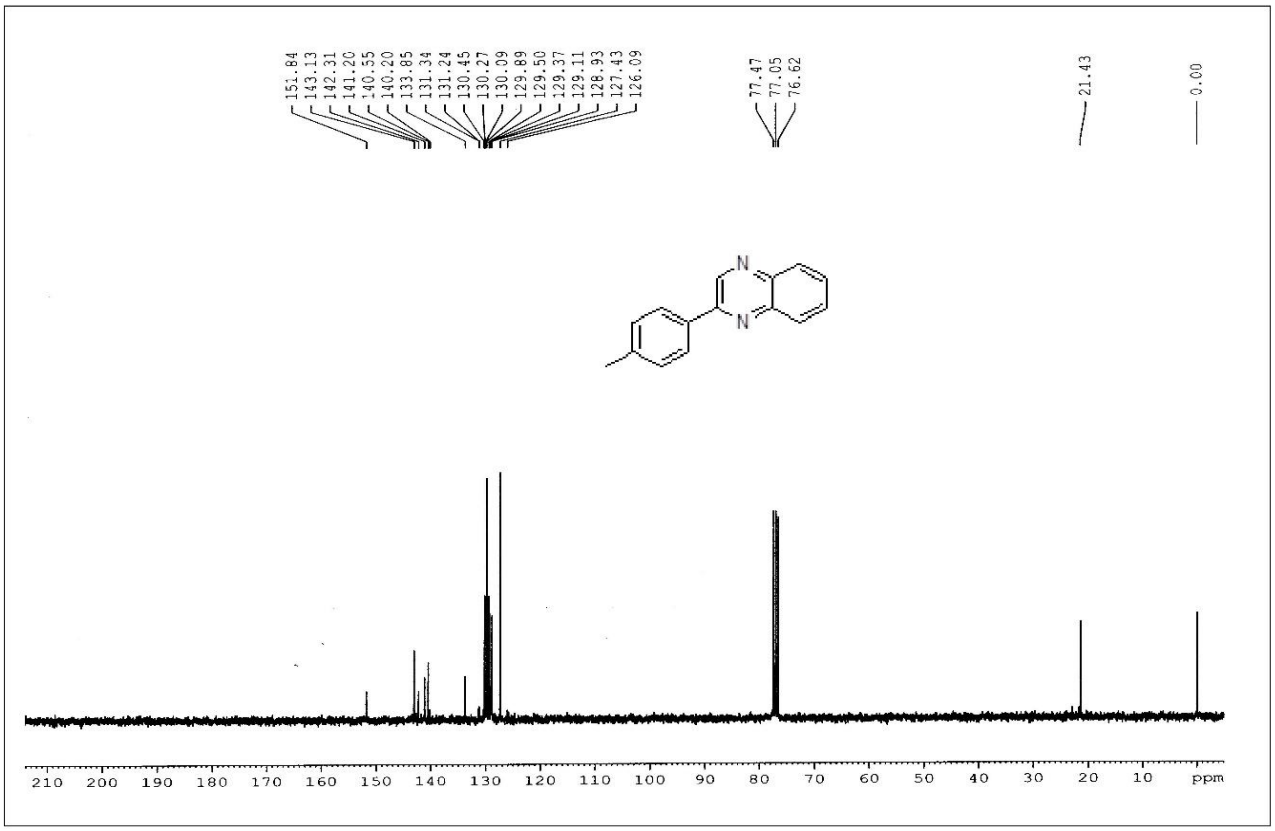


Fig. IV. B. 12. ^{1}H and ^{13}C NMR spectra of 2-*p*-Tolylquinoxaline

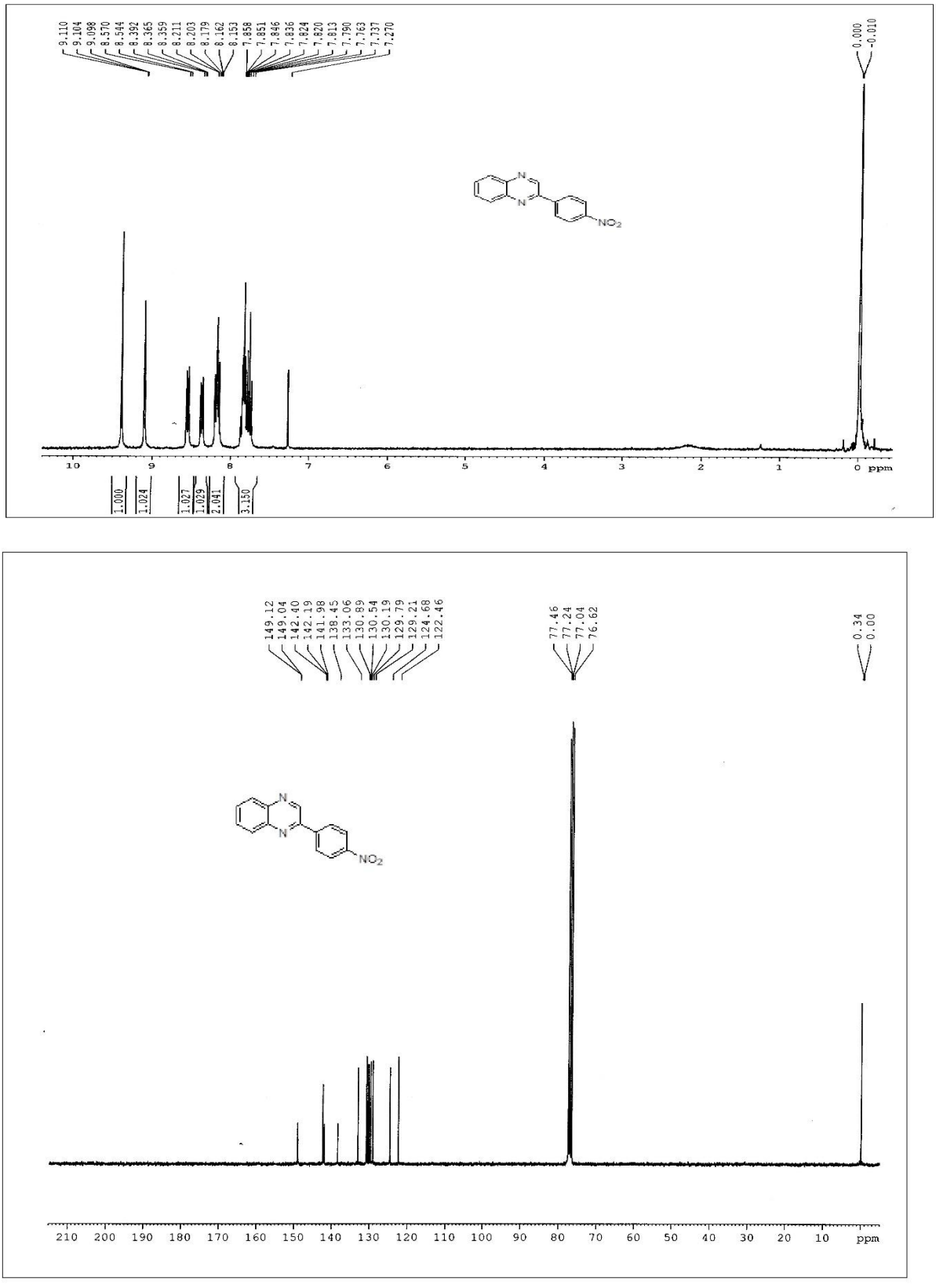


Fig. IV. B. 13. ^{1}H and ^{13}C NMR spectra of 2-(4-Nitrophenyl) quinoxaline

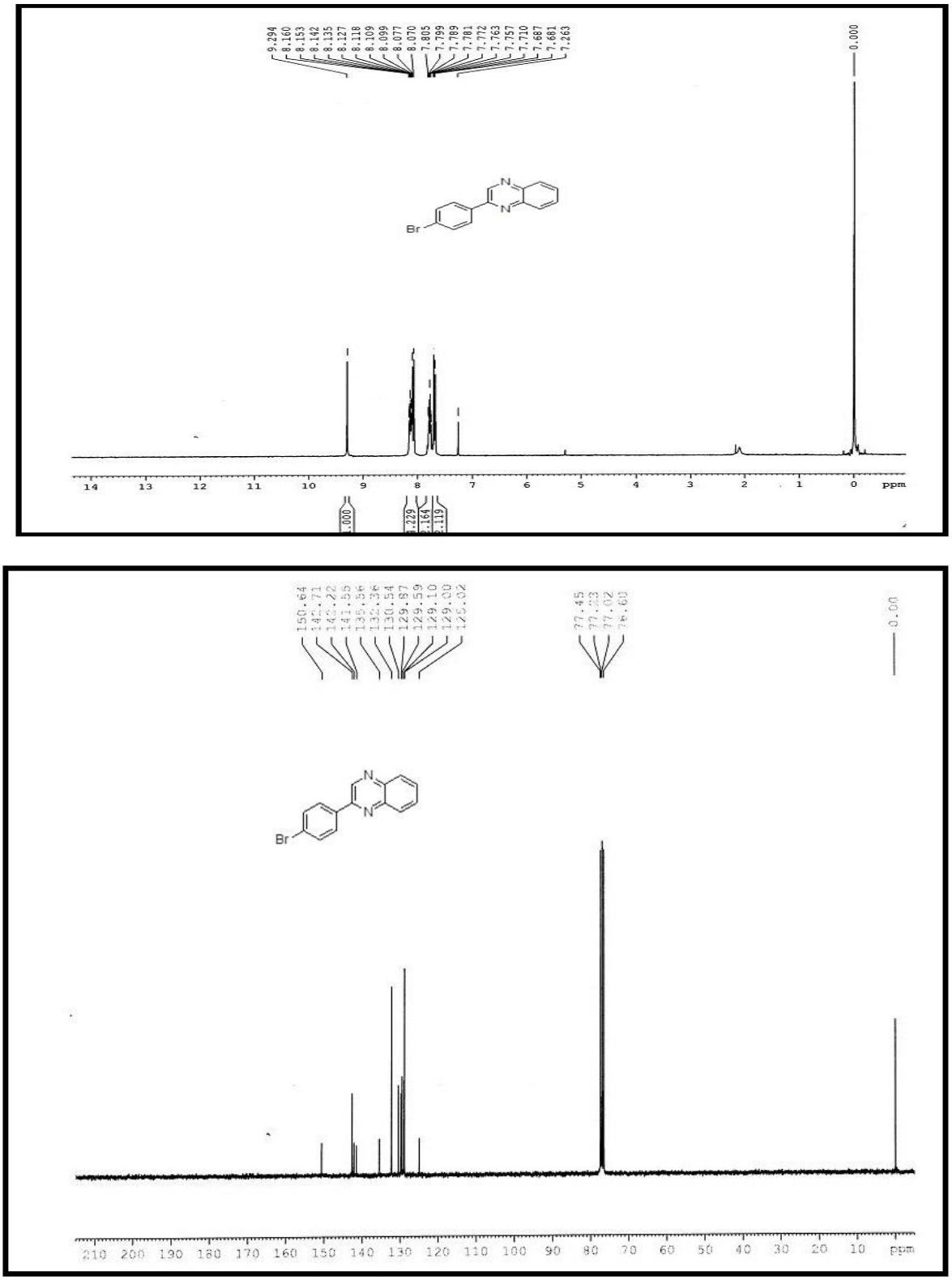


Fig. IV. B. 14. ^{1}H and ^{13}C NMR spectra of 2-(4-Bromophenyl) quinoxaline

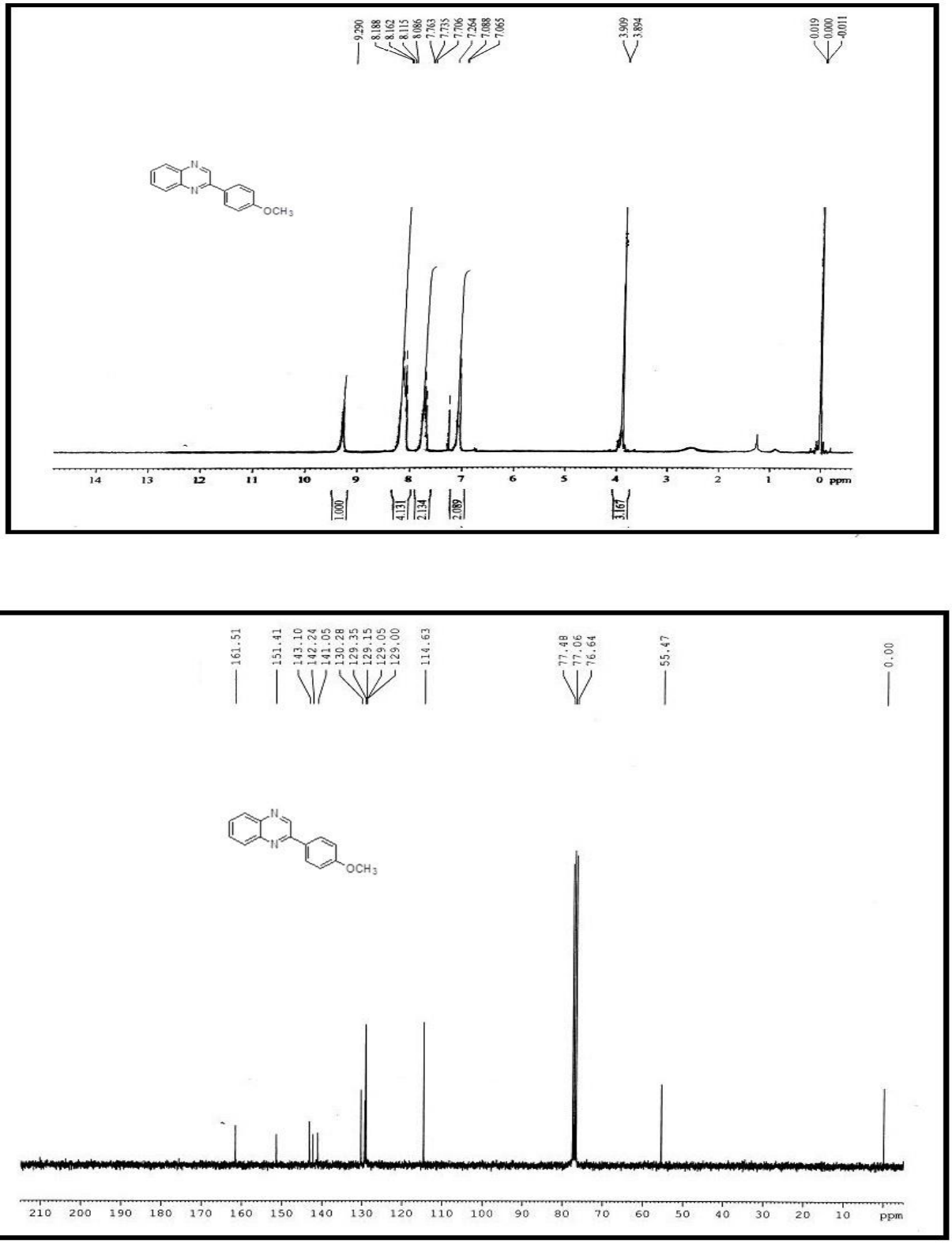


Fig. IV. B. 15. ^{1}H and ^{13}C NMR spectra of 2-(4-Methoxyphenyl) quinoxaline

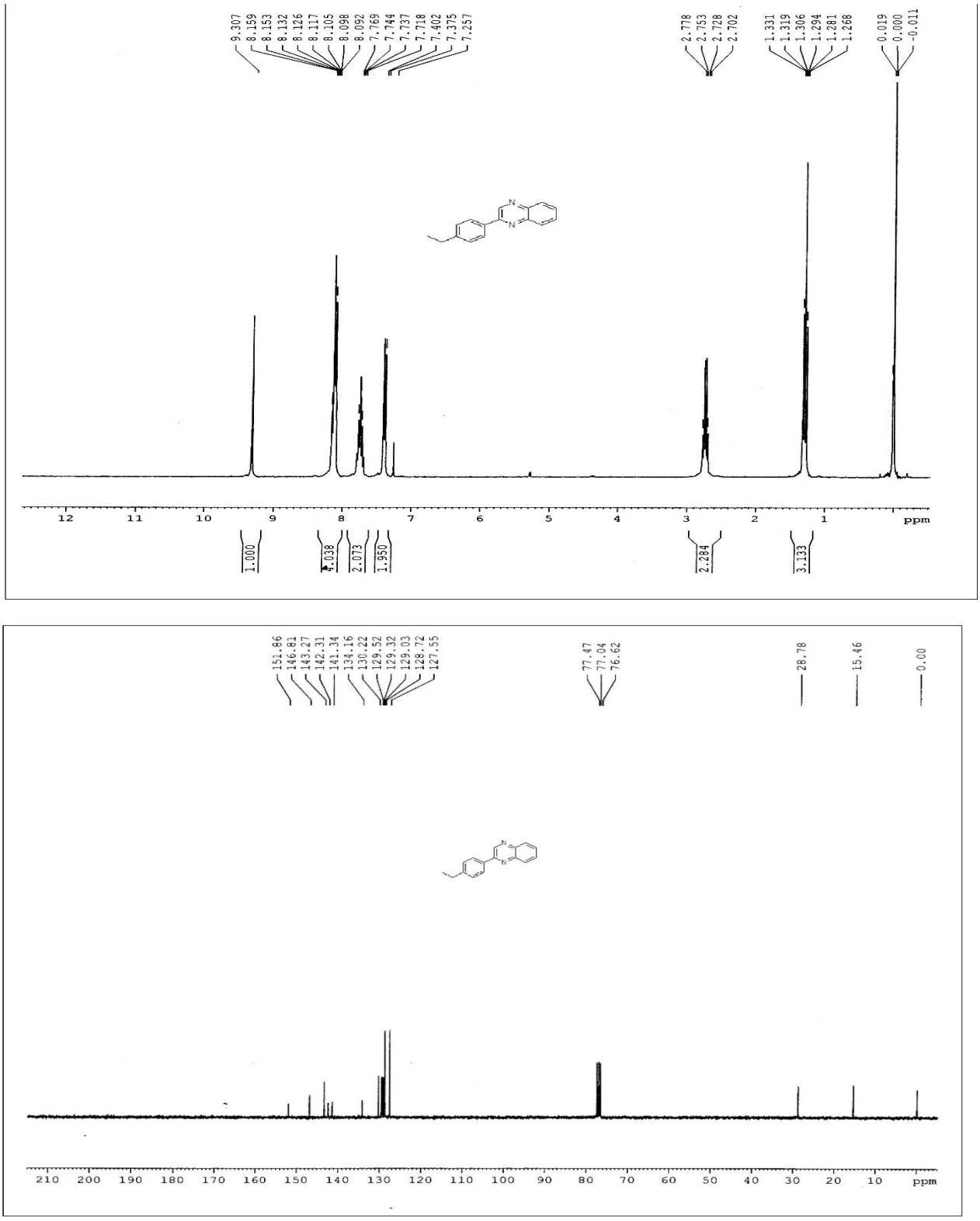


Fig. IV. B. 16. ^{1}H and ^{13}C NMR spectra of 2-(4-Ethylphenyl) quinoxaline

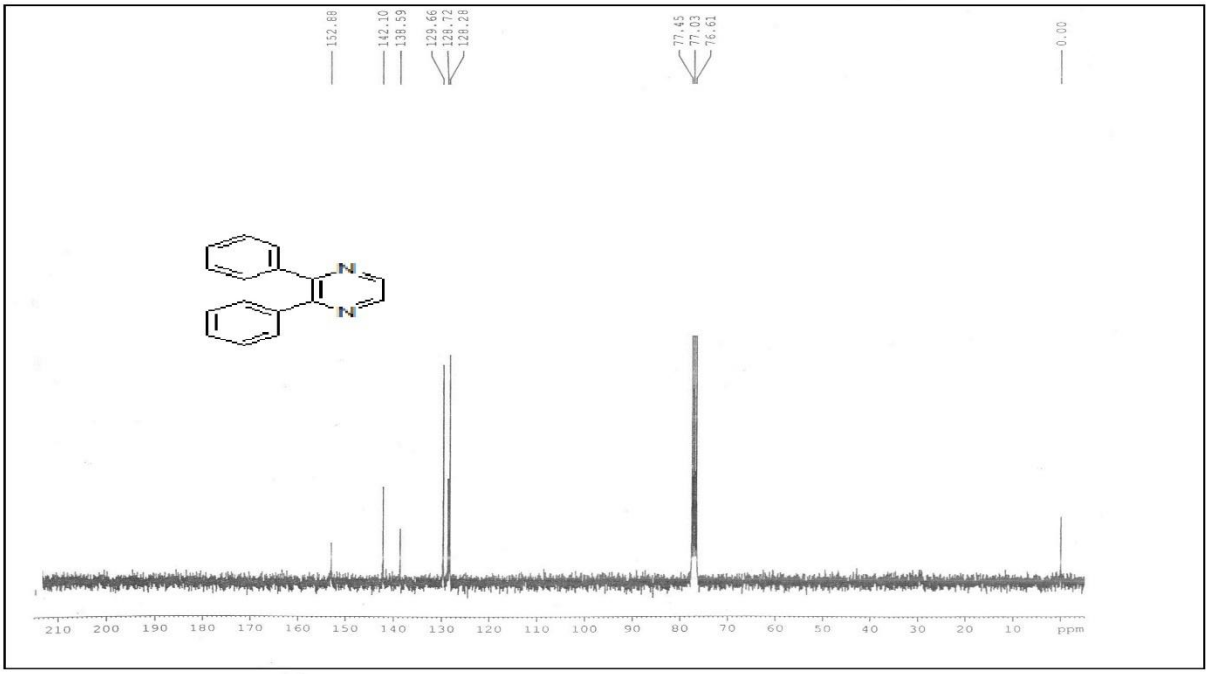


Fig. IV. B. 17. ^{1}H and ^{13}C NMR spectra of 2,3-diphenylpyrazine

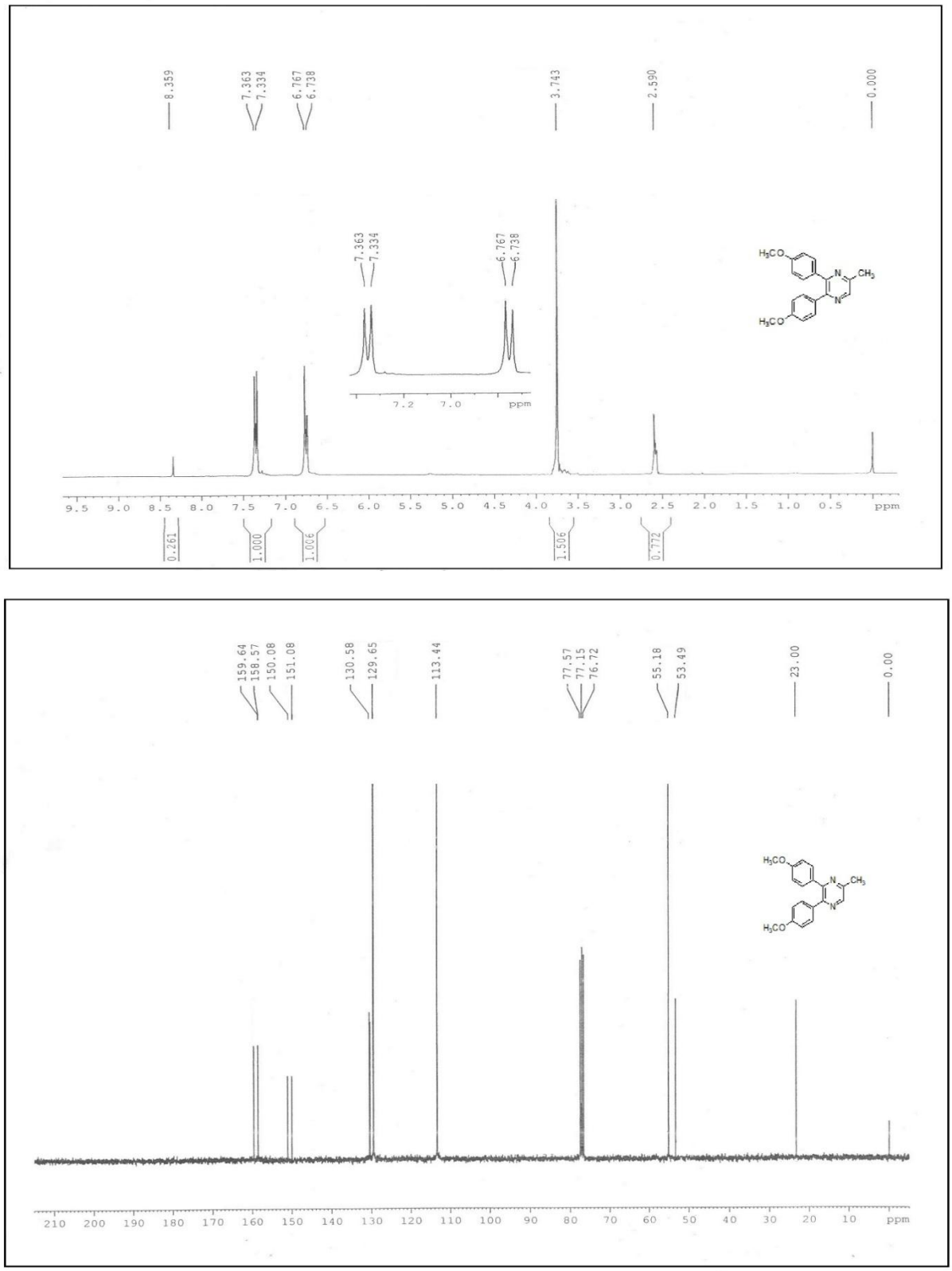


Fig. IV. B. 18. ^{1}H and ^{13}C NMR spectra of 2, 3-bis (4-methoxyphenyl)-5-methylpyrazine

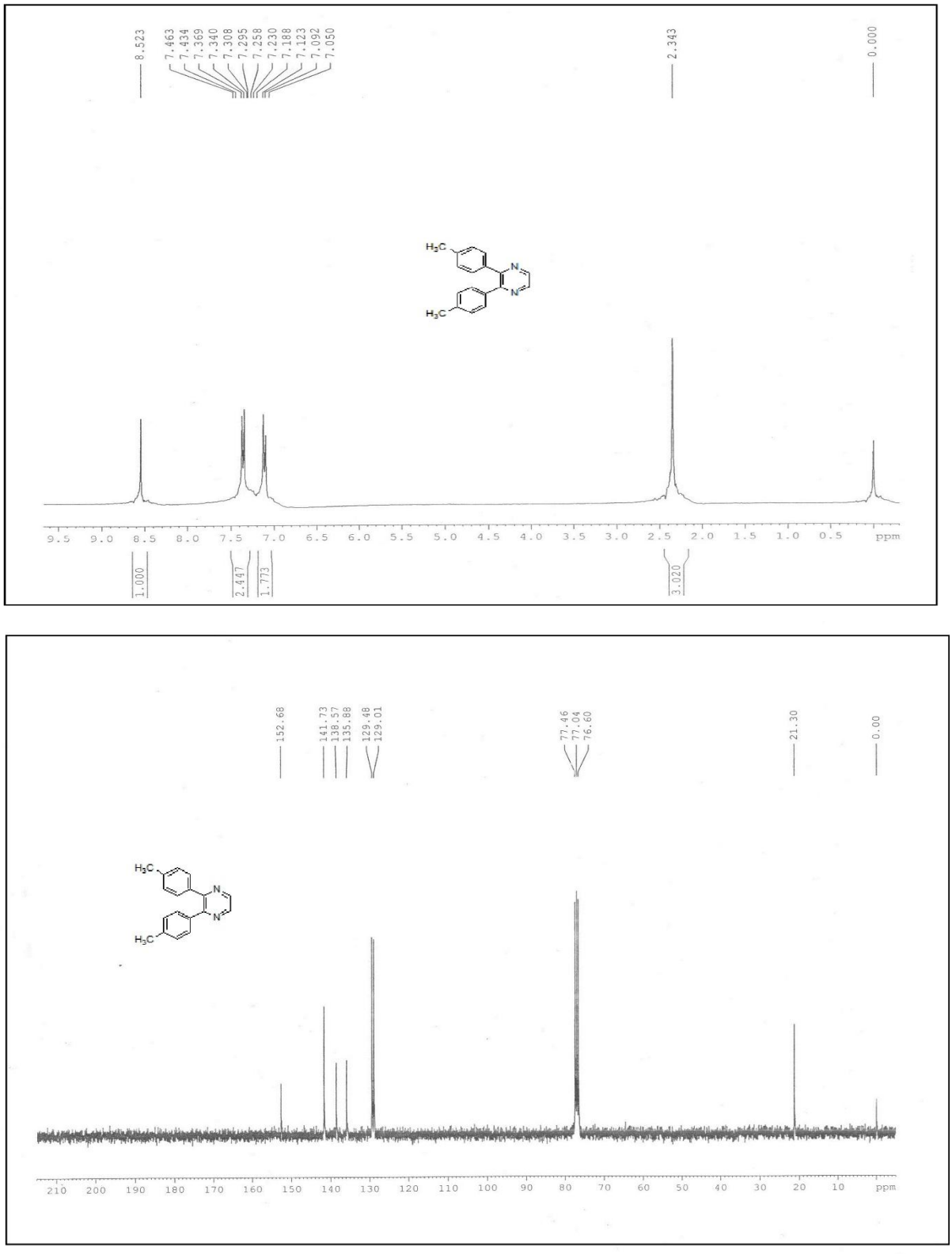
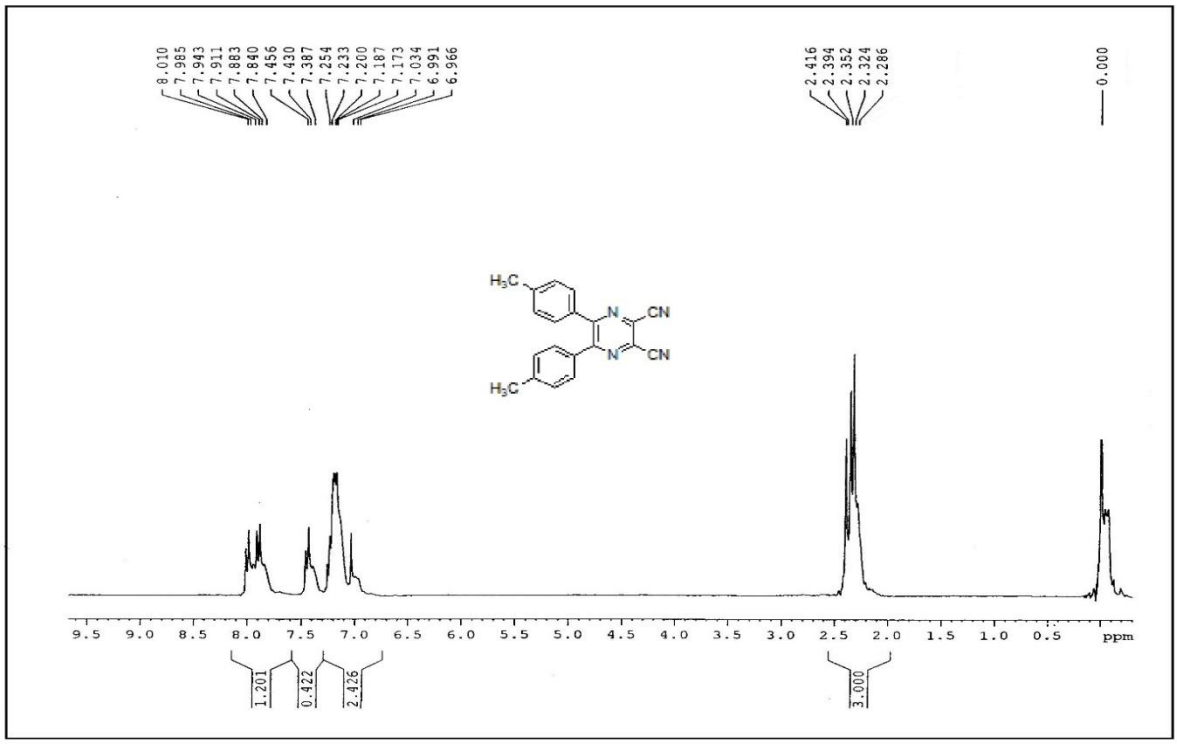


Fig. IV. B. 19. ^{1}H and ^{13}C NMR spectra of 2,3-di*p*-tolylpyrazine



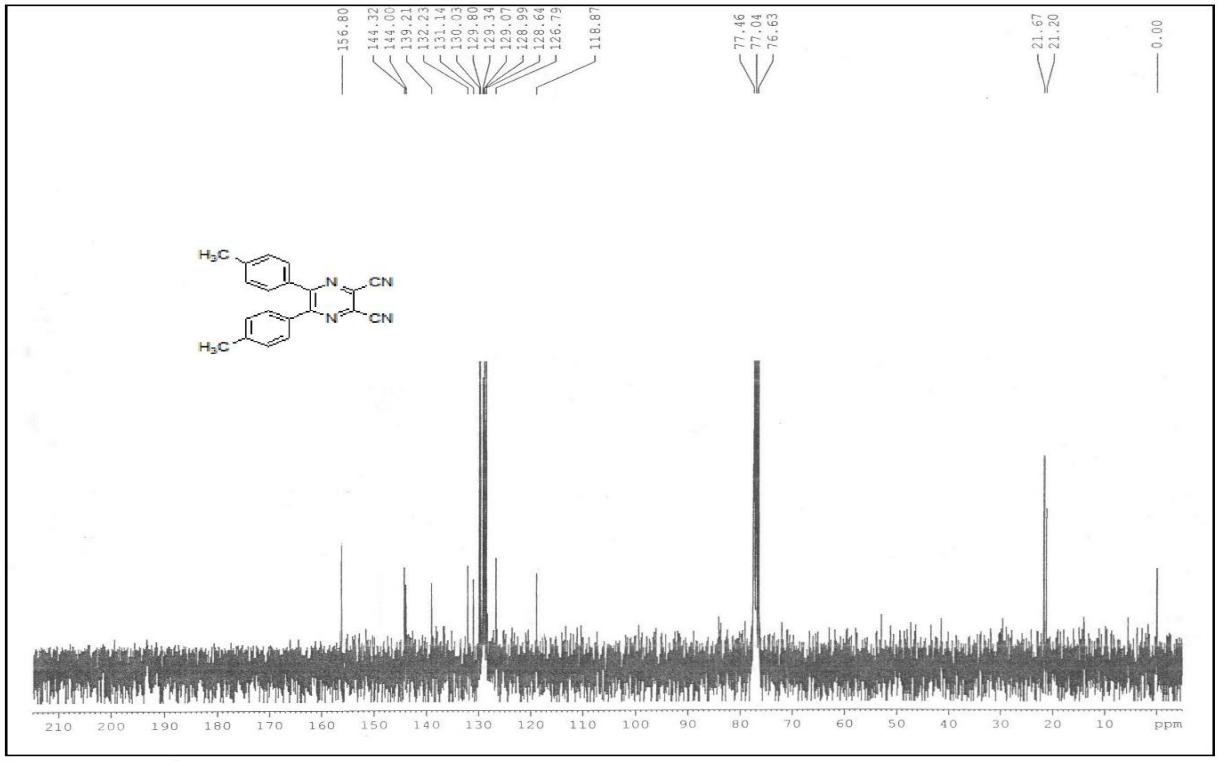
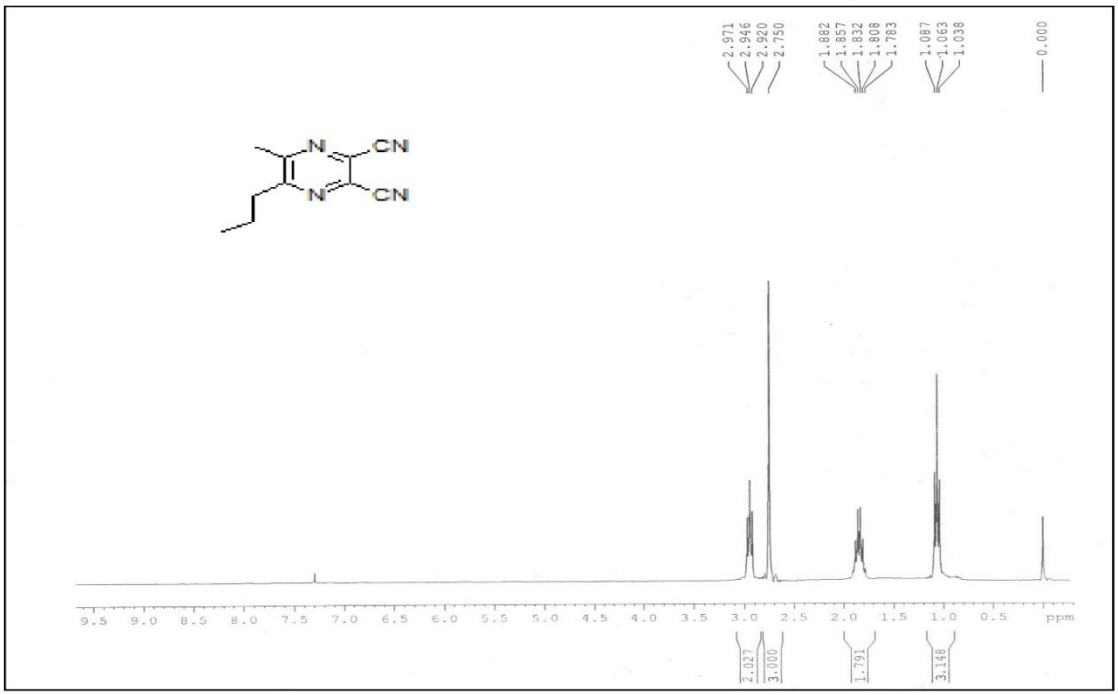


Fig. IV. B. 20. ^{1}H and ^{13}C NMR spectra of 5, 6-di*p*-tolylpyrazine-2,3-dicarbonitrile



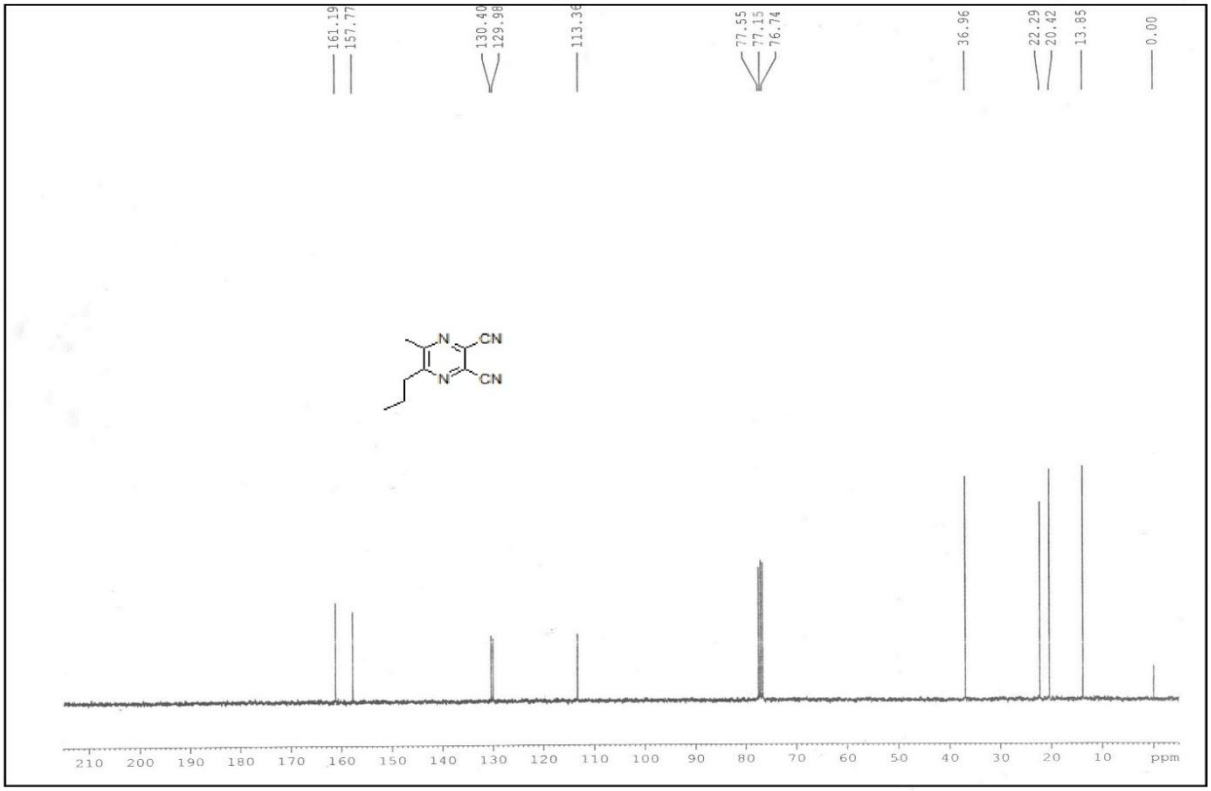
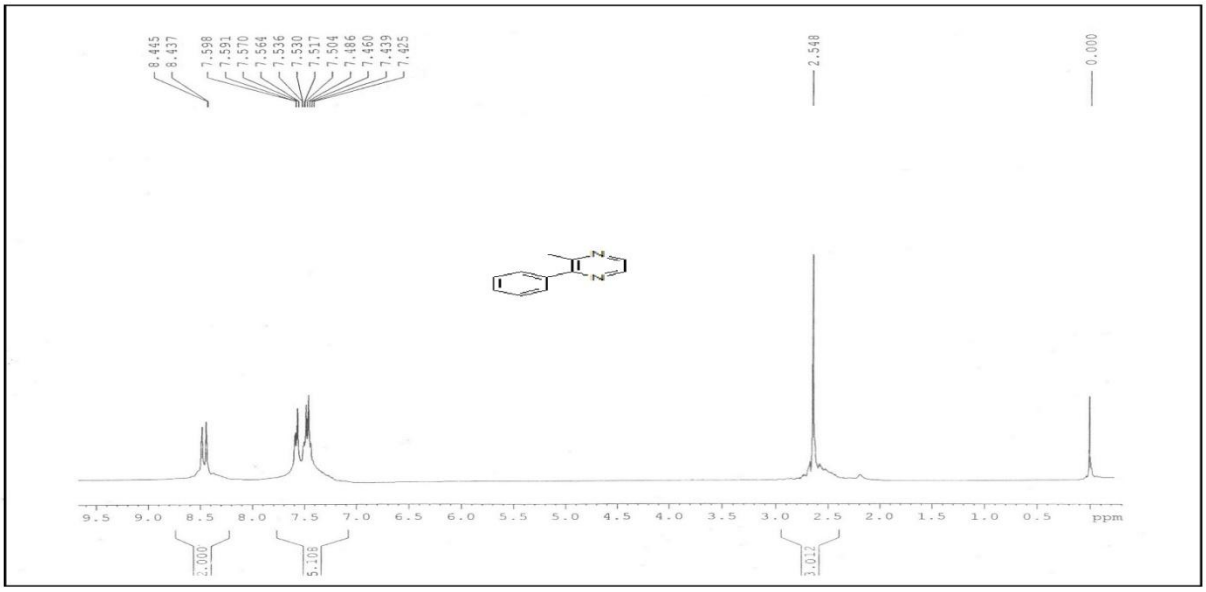


Fig. IV. B. 21. ^{1}H and ^{13}C NMR spectra of 5-methyl-6-propylpyrazine-2,3-dicarbonitrile



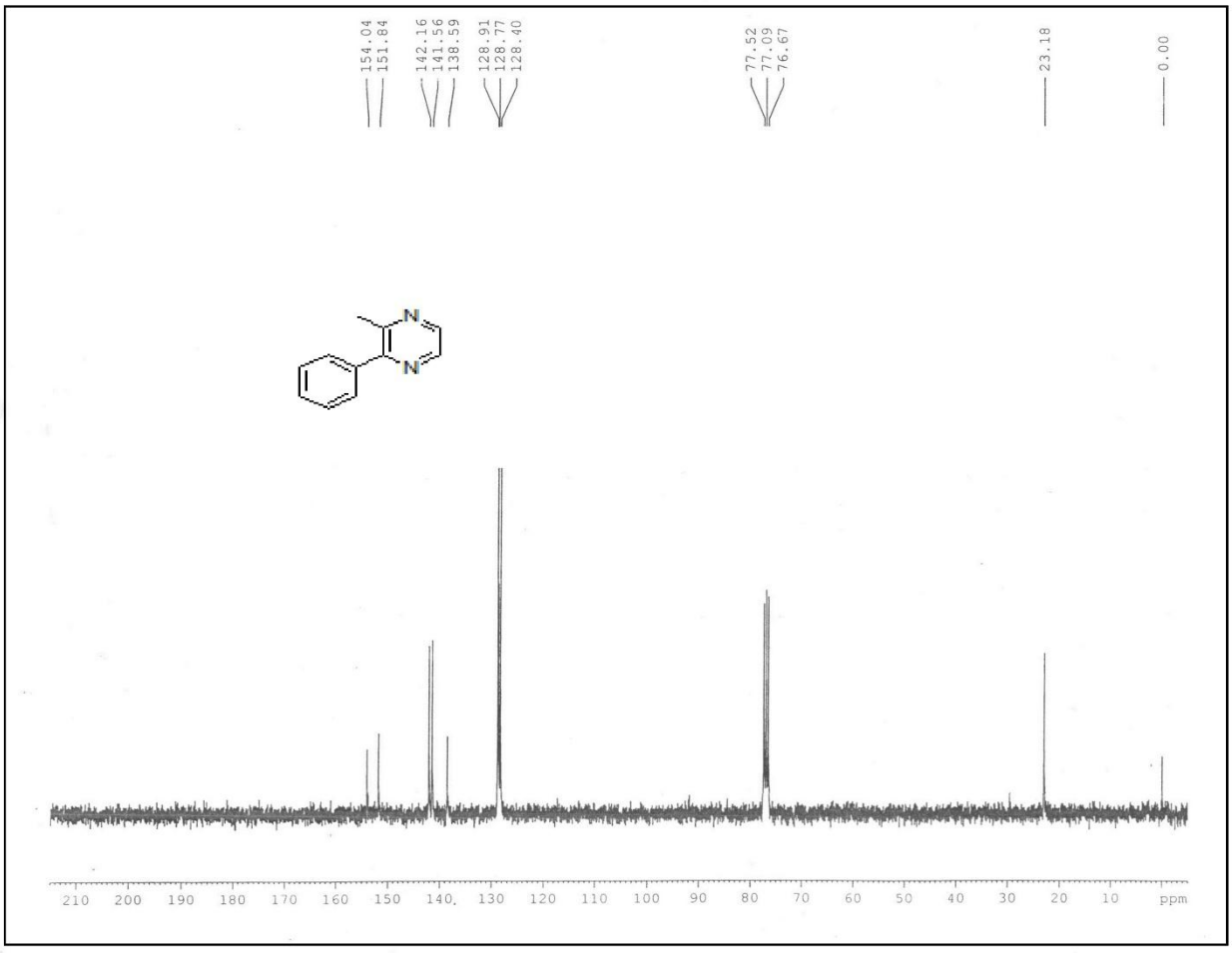


Fig. IV. B. 22. ^{1}H and ^{13}C NMR spectra of 2-Methyl-3-phenylpyrazine

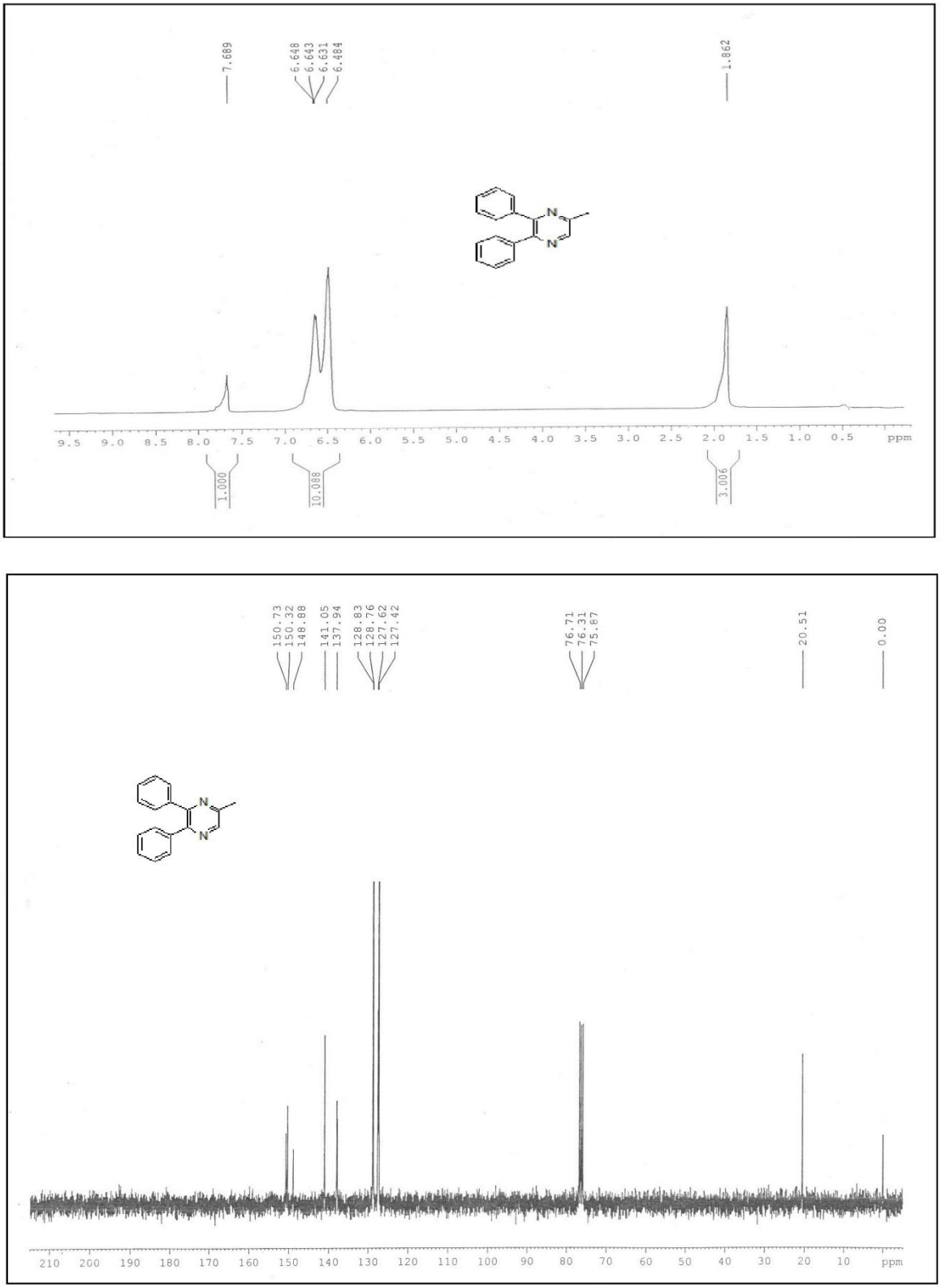


Fig. IV. B. 23. ^{1}H and ^{13}C NMR spectra of 5-Methyl-2,3-diphenylpyrazine

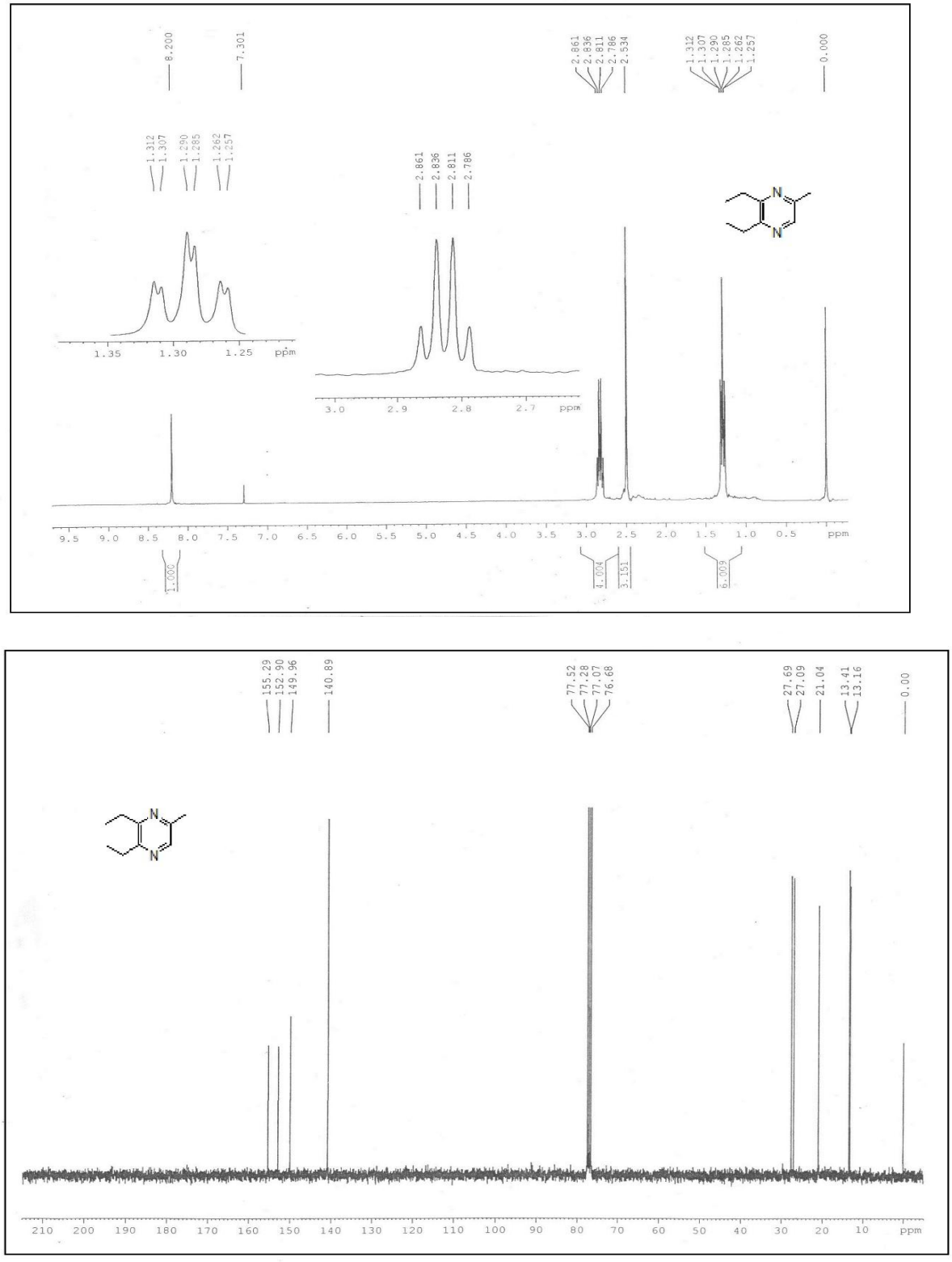


Fig. IV. B. 24. ^{1}H and ^{13}C NMR spectra of 2, 3-Diethyl-5-methylpyrazine

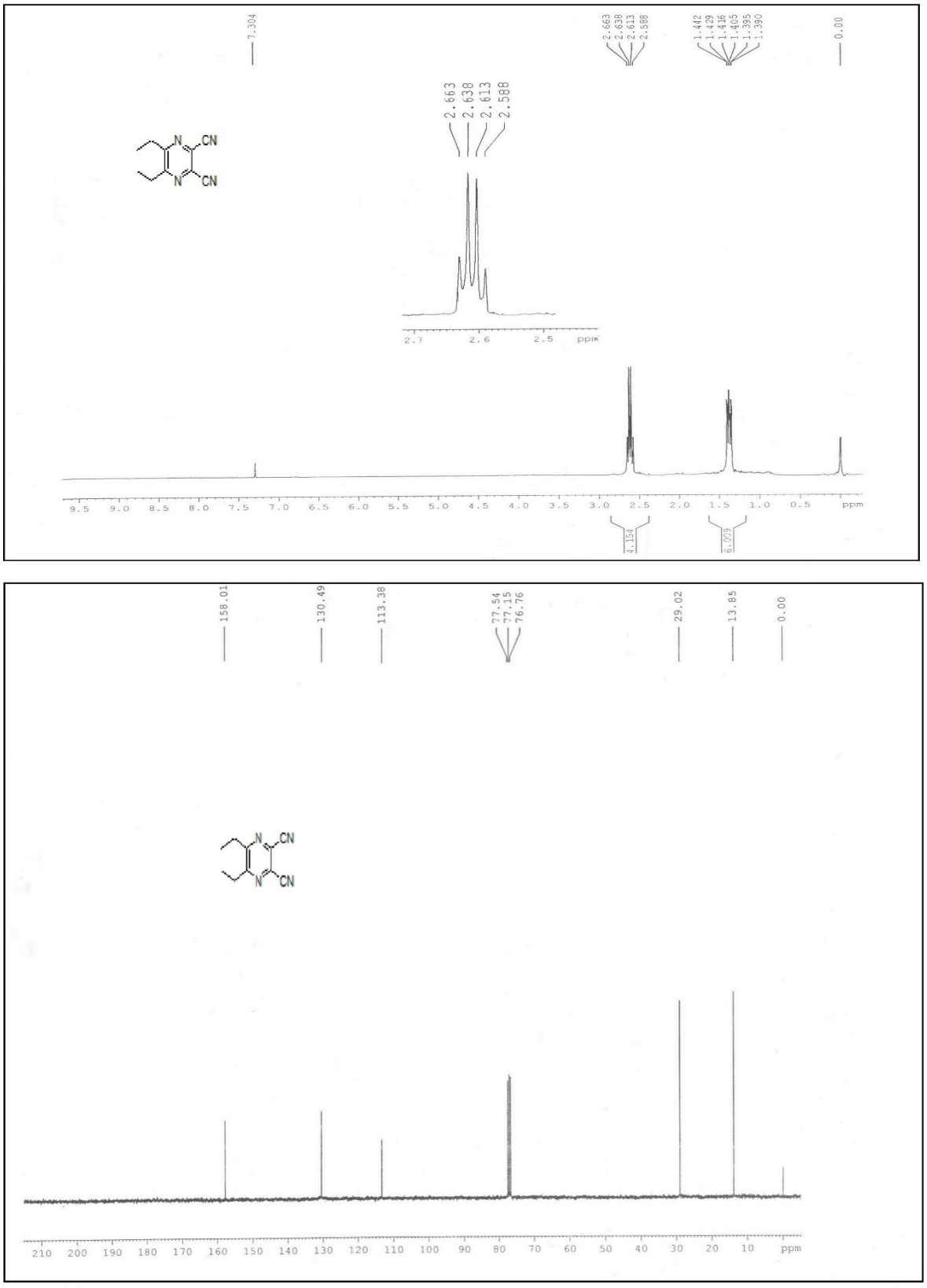


Fig. IV. B. 25. ^{1}H and ^{13}C NMR spectra of 5, 5-Diethylpyrazine-2,3-dicarbonitrile

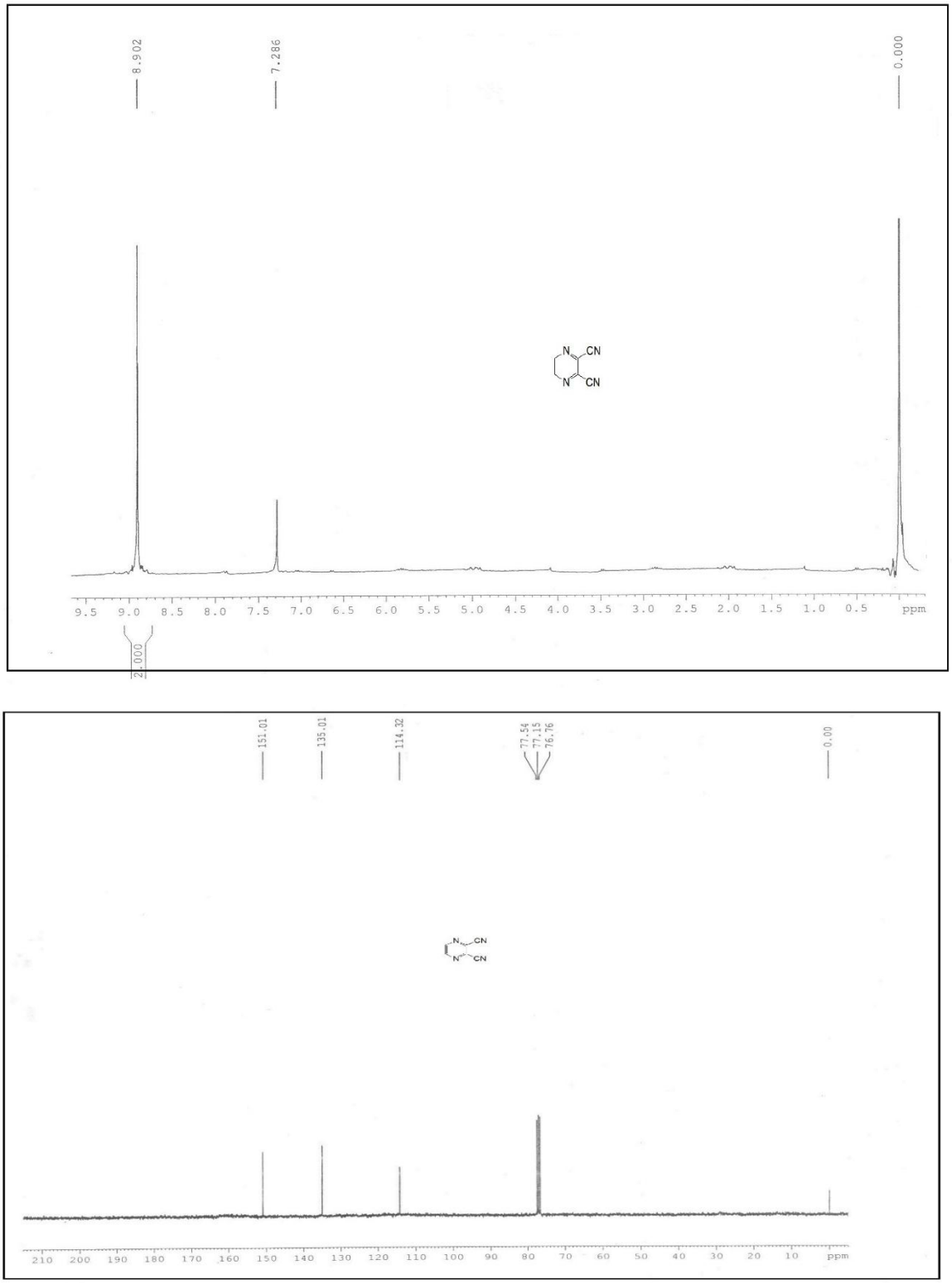


Fig. IV. B. 26. ^{1}H and ^{13}C NMR spectra of Pyrazine-2,3-dicarbonitrile

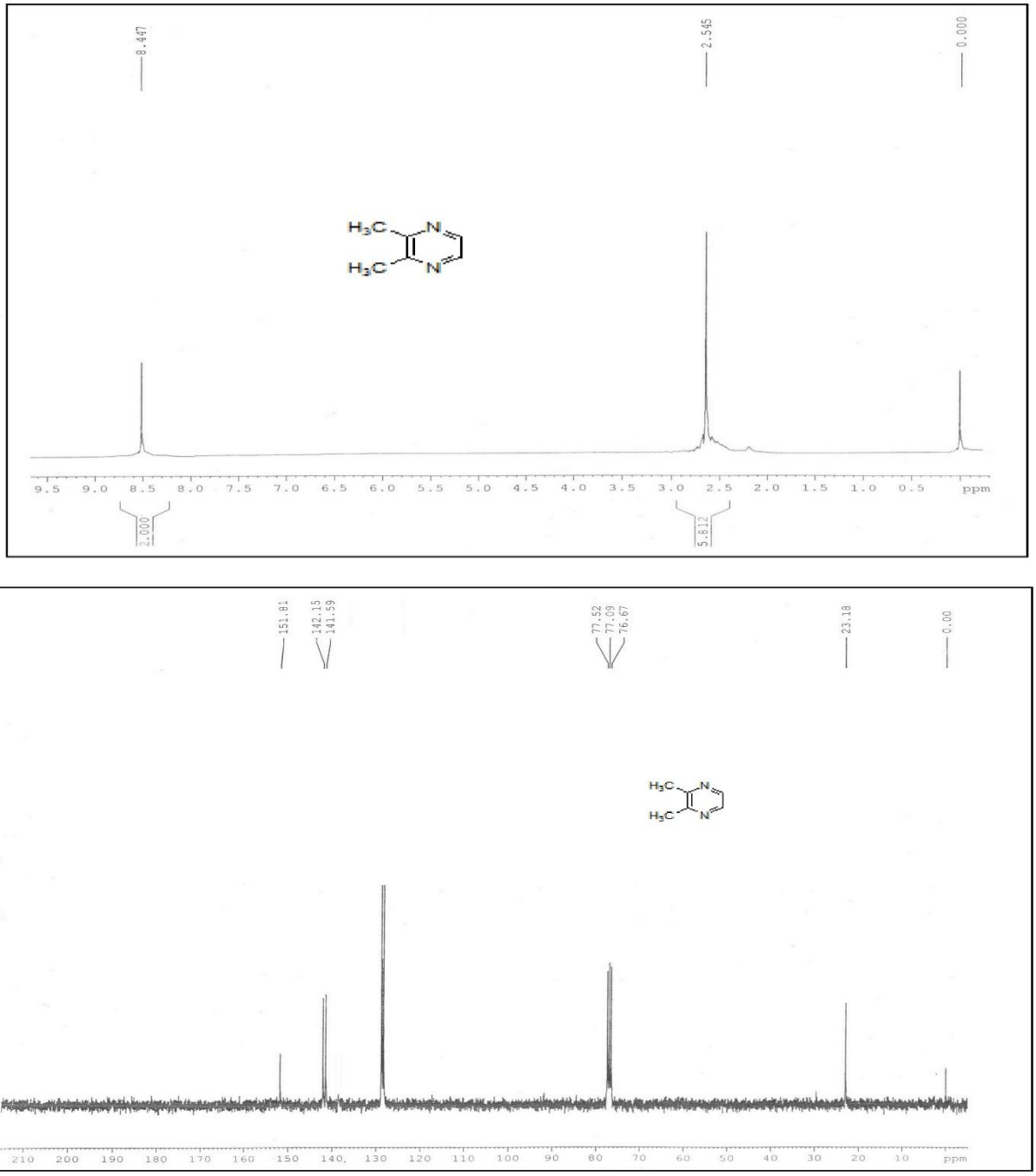


Fig. IV. B. 27. ^{1}H and ^{13}C NMR spectra of 2, 3-Dimethyl pyrazine

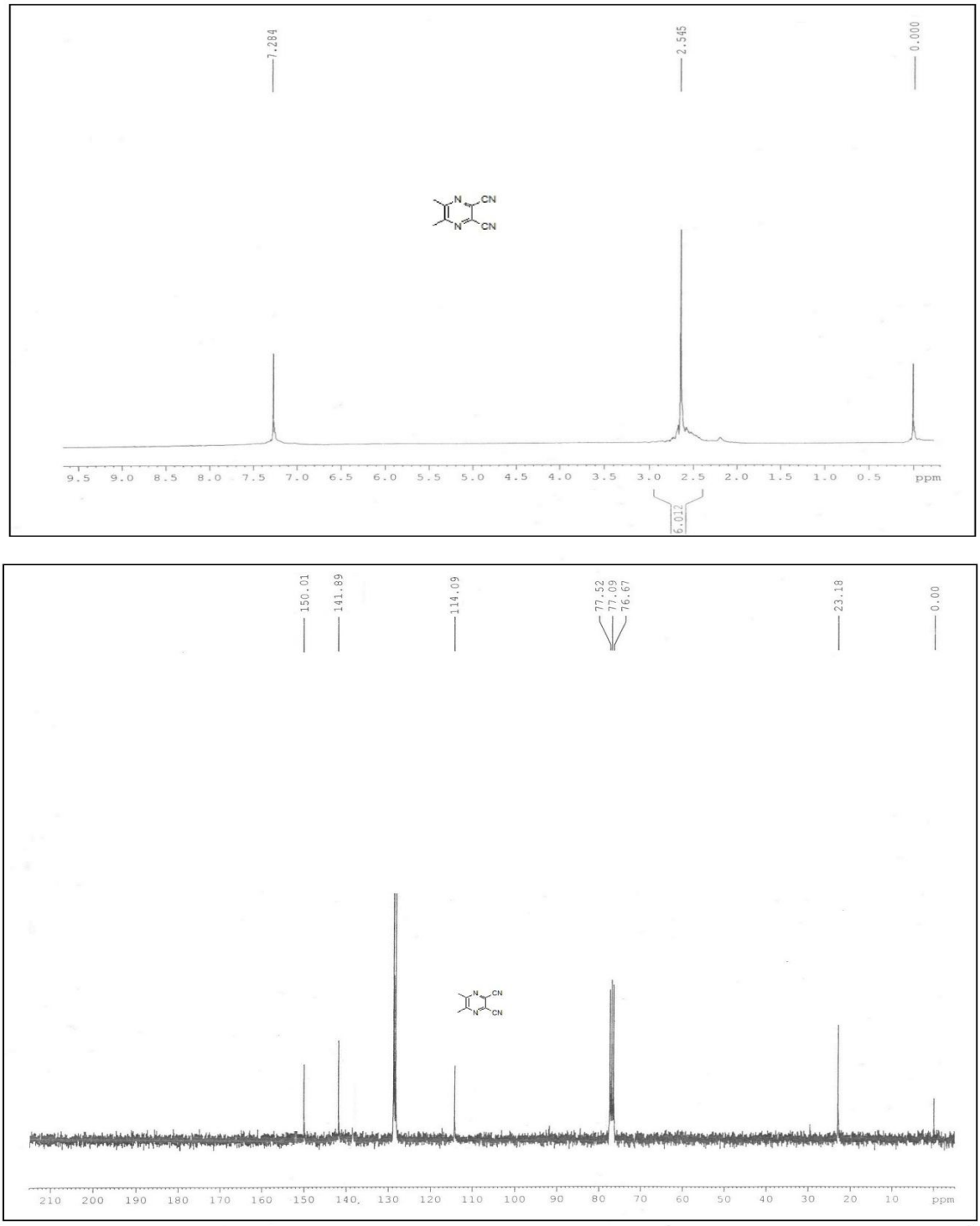


Fig. IV. B. 28^{1}H and ^{13}C NMR spectra of 5, 6-dimethylpyrazine-2,3-dicarbonitrile

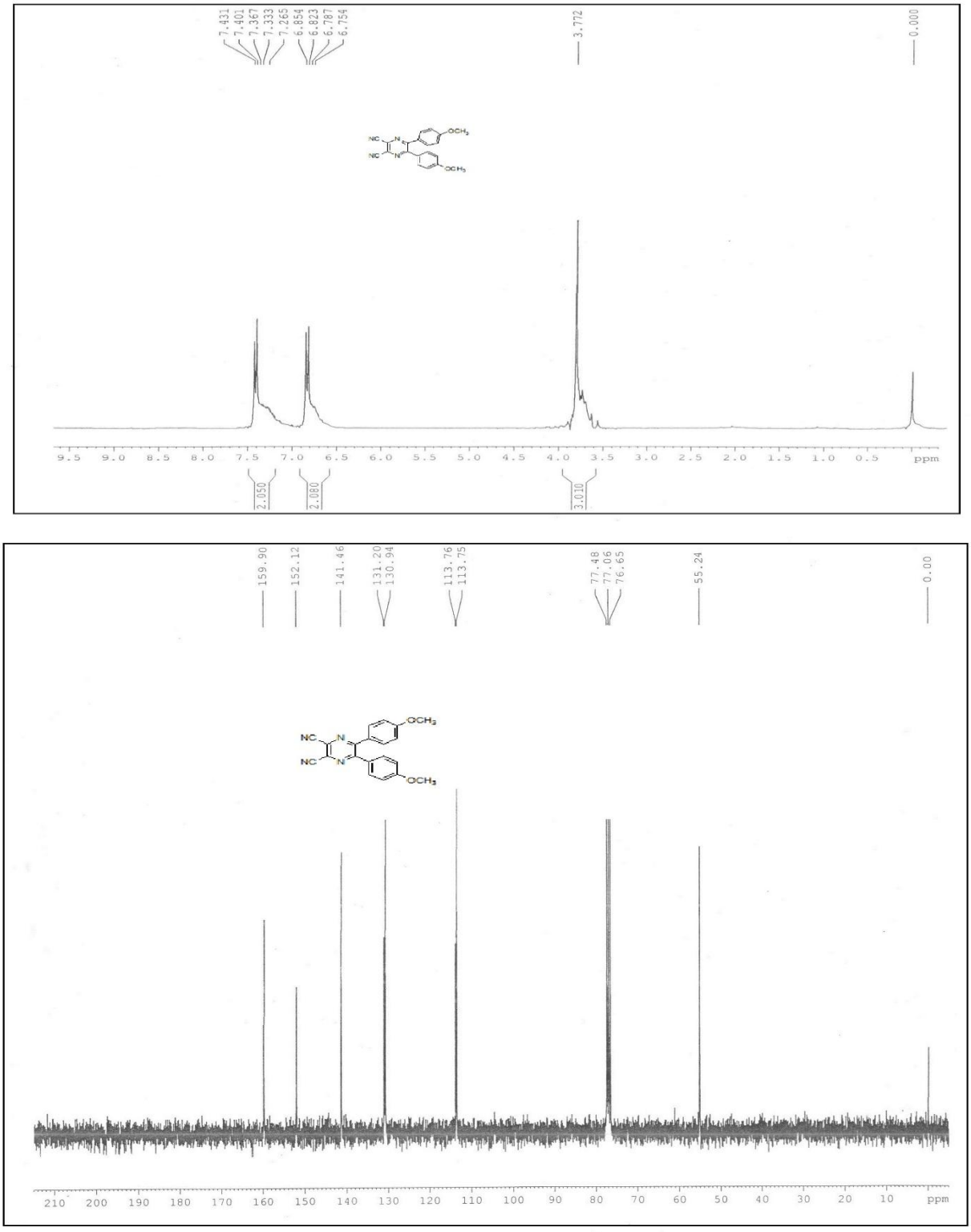


Fig. IV. B. 29. ^{1}H and ^{13}C NMR spectra of bis-(4-methoxyphenyl) pyrazine-2,3-dicarbonitrile

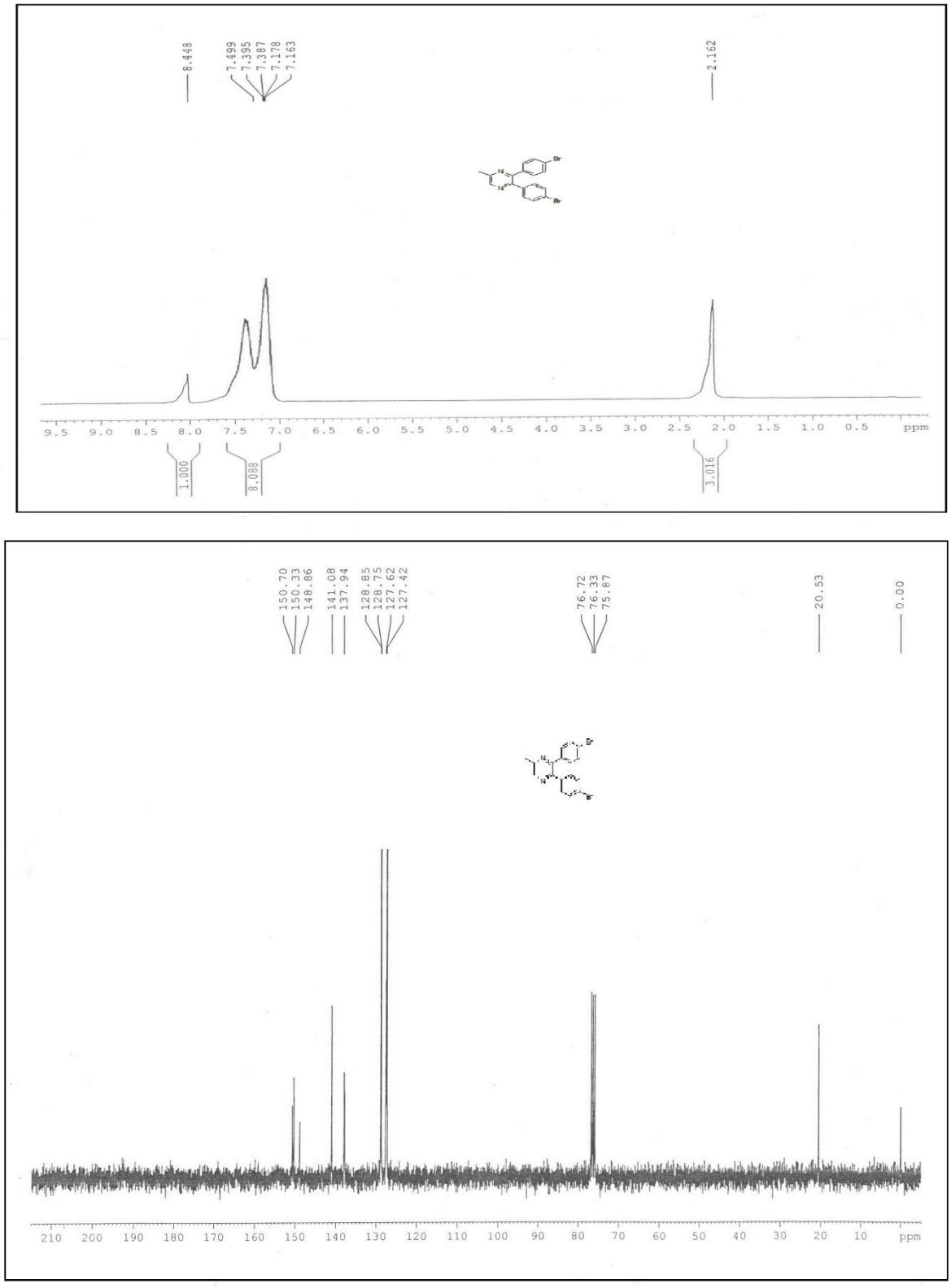
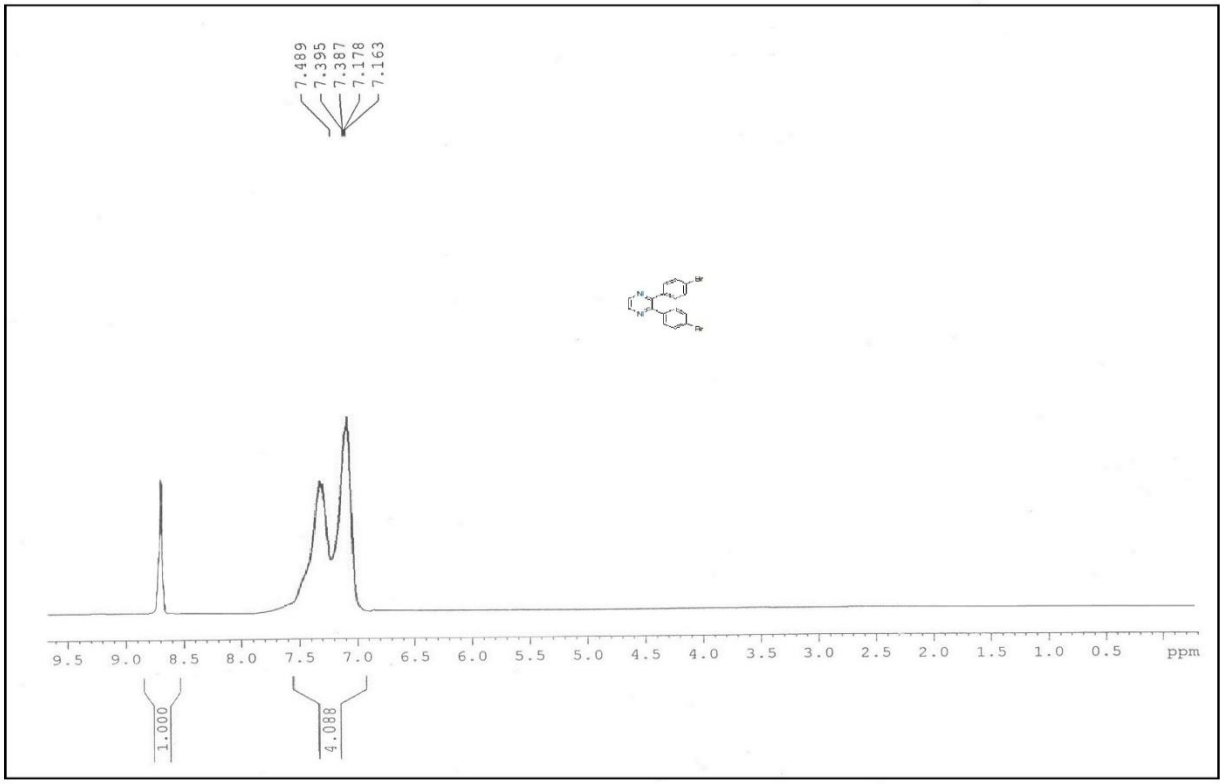


Fig. IV. B. 30. ^{1}H and ^{13}C NMR spectra of 2, 3-bis-(4-bromophenyl)-5-methylpyrazine



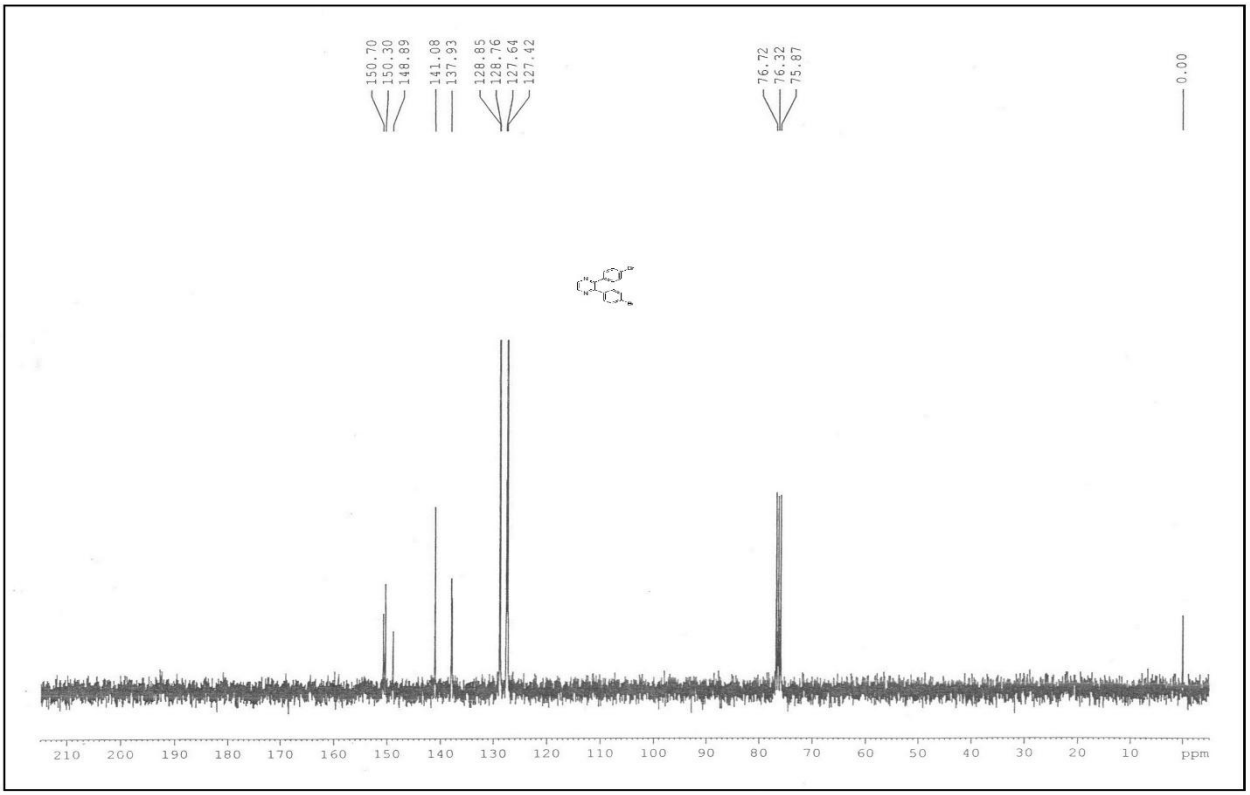
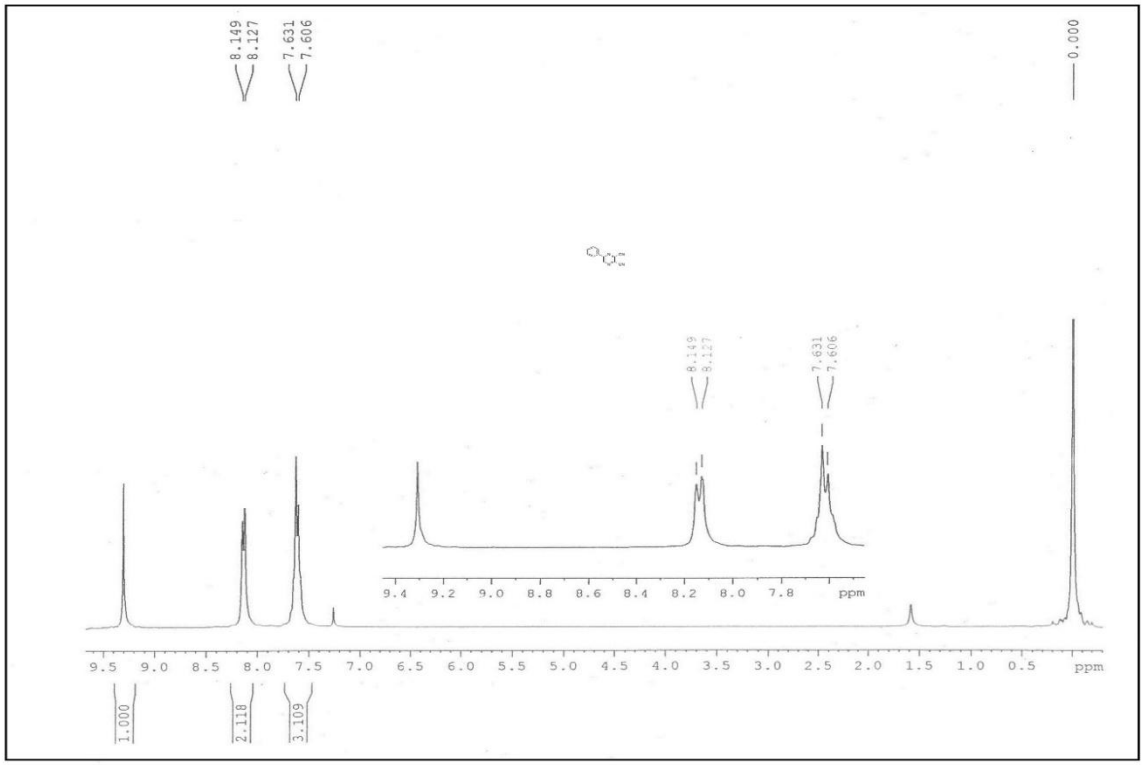


Fig. IV. B. 31. ^{1}H and ^{13}C NMR spectra of 2, 3-bis-(4-bromophenyl)-pyrazine



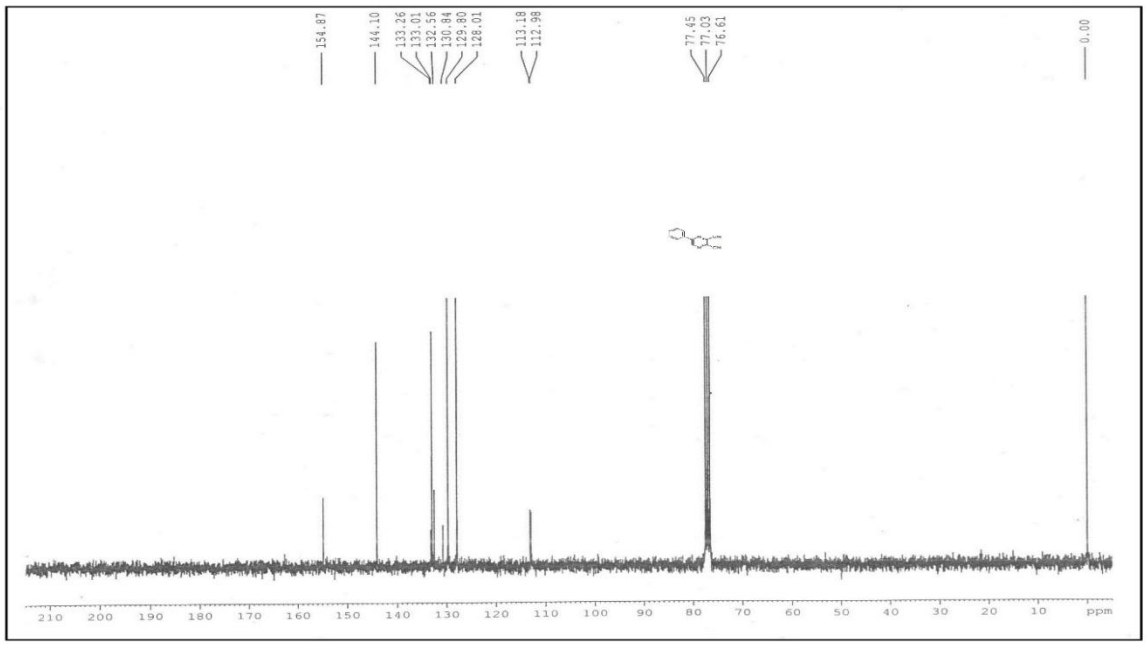
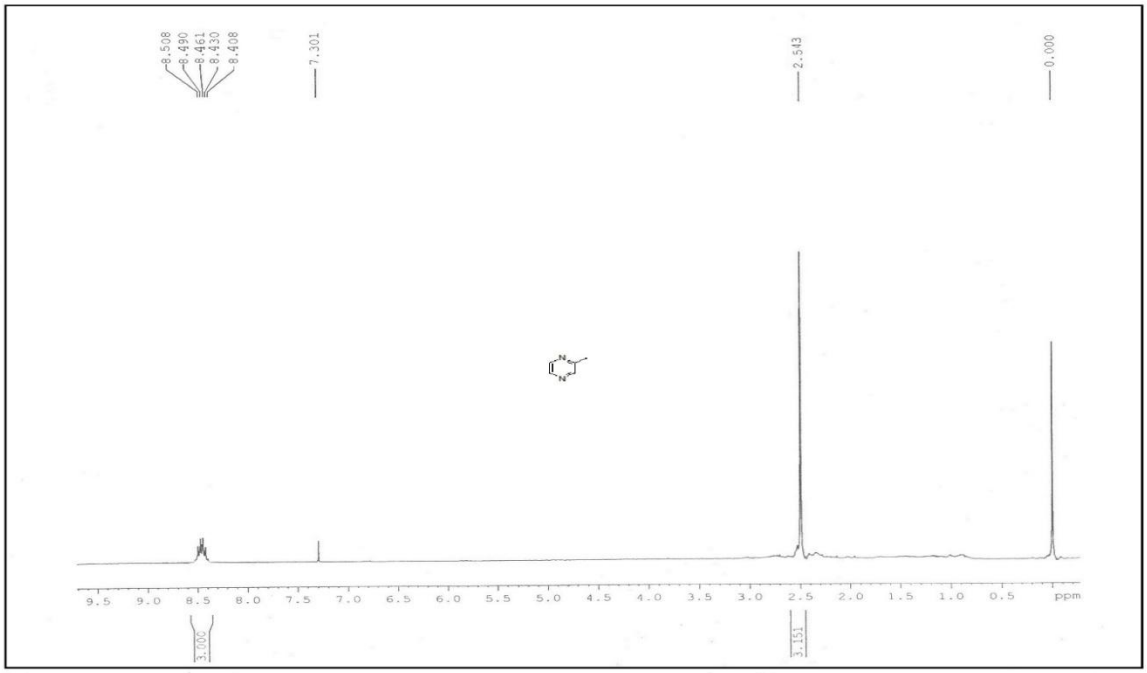


Fig. IV. B. 32. ^{1}H and ^{13}C NMR spectra of 5-phenylpyrazine-2,3-dicarbonitrile



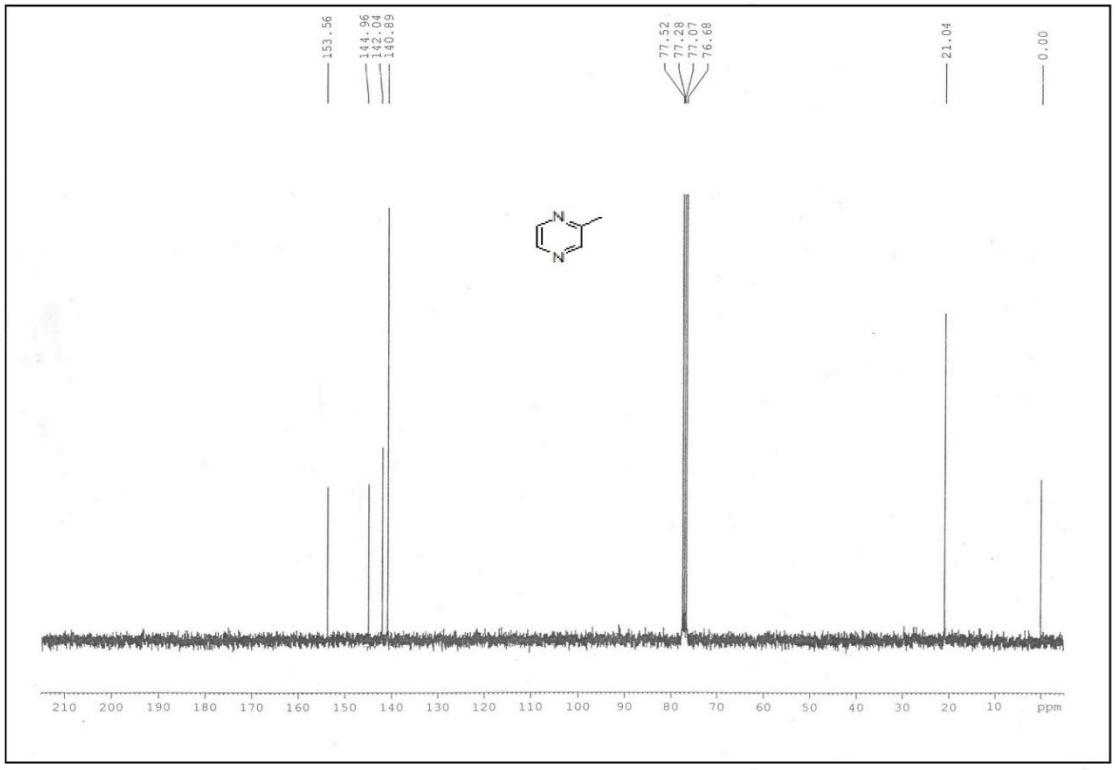
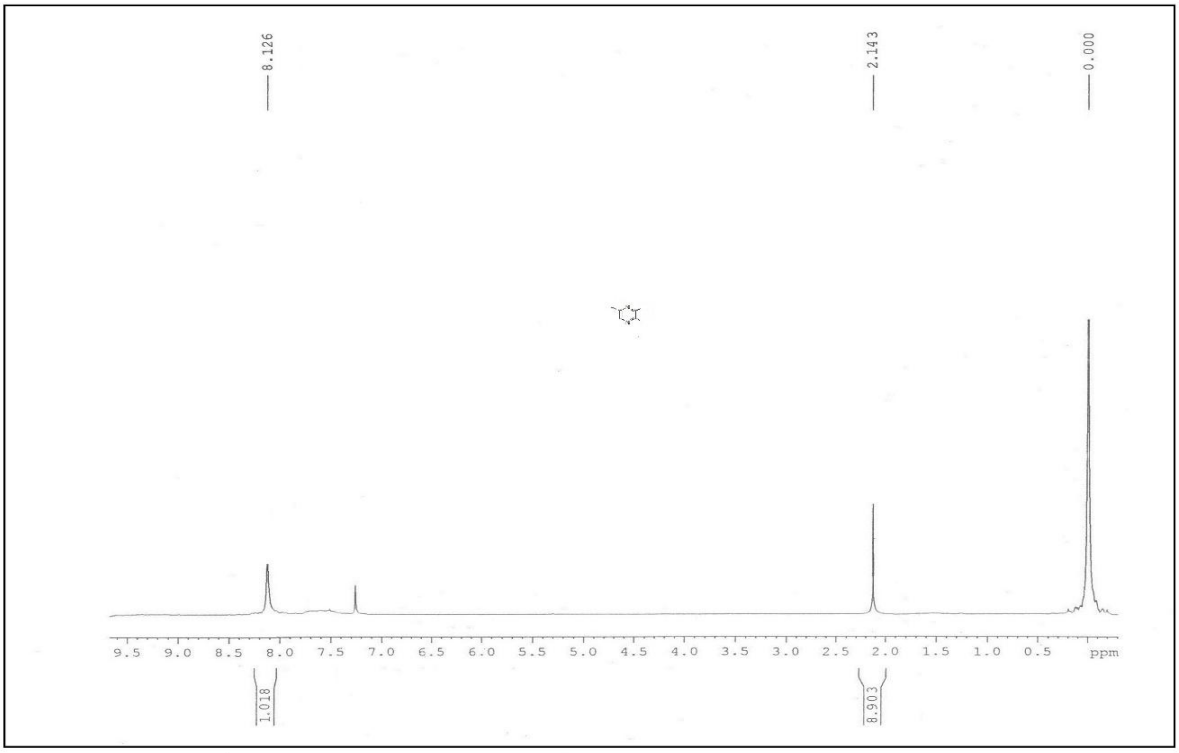


Fig. IV. B. 33. ^{1}H and ^{13}C NMR spectra of 2-methylpyrazine



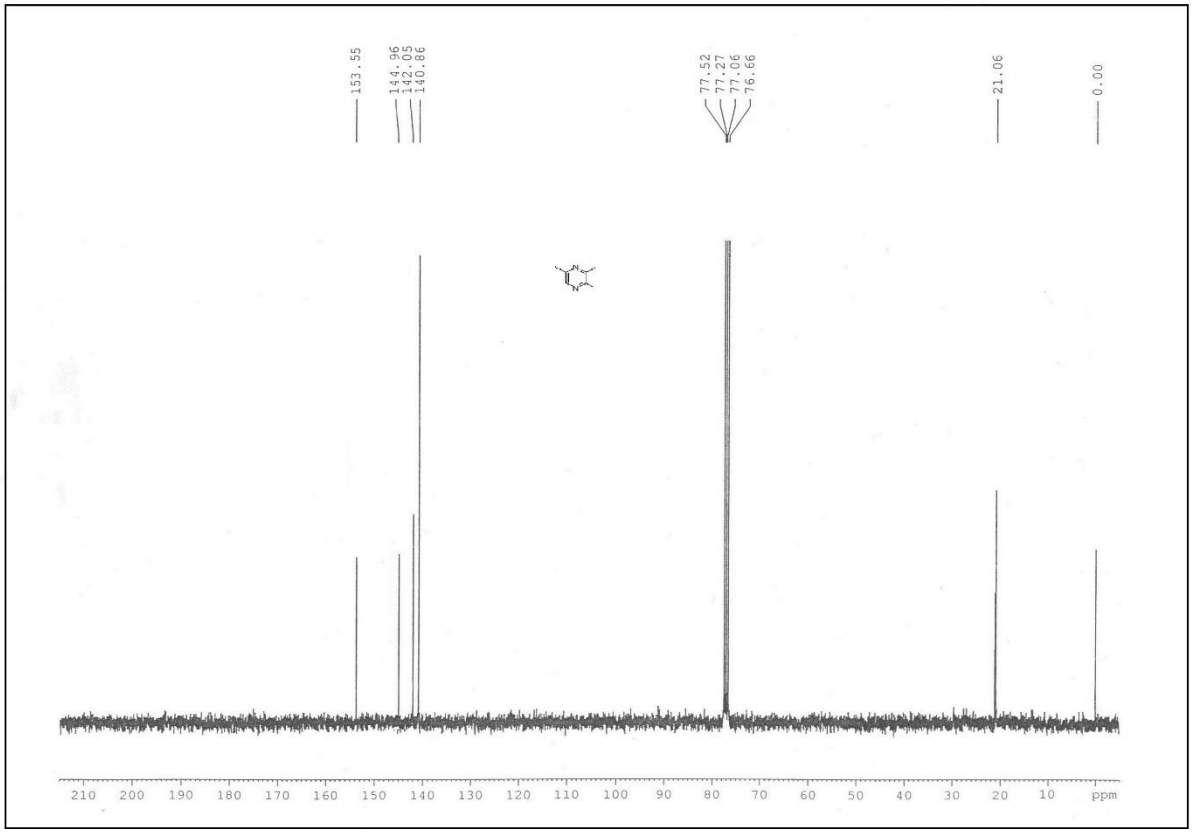


Fig. IV. B. 34. ^{1}H and ^{13}C NMR spectra of 2, 3, 5-trimethylpyrazine

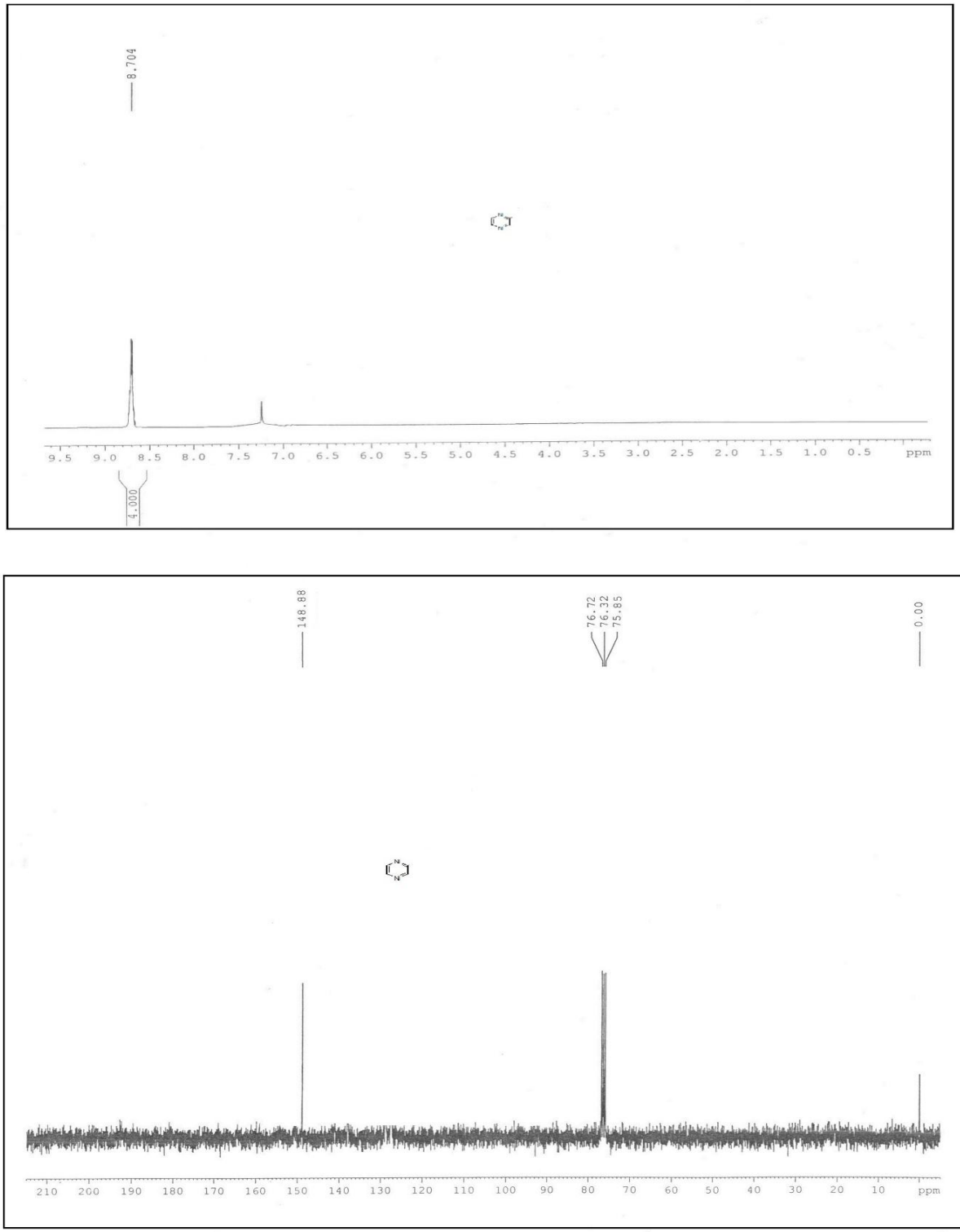


Fig. IV. B. 35. ^{1}H and ^{13}C NMR spectra of Pyrazine

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Fe_3O_4-nanoparticles catalyzed an efficient synthesis of nitriles from aldehydes

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ABSTRACT

Fe_3O_4-CTAB NPs have been applied as a competent catalyst for one-pot synthesis of nitriles directly from aldehydes. The present investigation describes the synthesis of nitriles by combination of aromatic/aliphatic/heterocyclic aldehydes and hydroxylamine hydrochloride in the presence of iron oxide nanocatalyst in DMF under reflux condition. Fe_3O_4-CTAB NPs were prepared by reported method and characterized by FE-SEM, TEM, and XRD analysis. The amount of Fe in Fe_3O_4-CTAB was quantified by Atomic Absorption Spectroscopy (AAS). The protocol endow with excellent yield of products along with simple reaction set up and economically adept alternative approach.

Introduction

Suitably design organonitrile derivatives are widely documented as bioactive molecules[1] (Fig. 1). Nitriles are also regarded as prominent intermediate for the production of various pharmaceuticals, agrochemicals, polymers, pigments, and dyes.[2] It's applications in heterocyclic compound synthesis and functional group transformations are well established from the long time.[3] Classically adopted methods for nitrile synthesis are Sandmeyer reaction,[4] ammoxidation of aldehydes,[5] Kolbe nitrile synthesis,[6] hydrocyanation of alkenes,[7] and Rosenmund–von Braun reaction.[8] Moreover, various methodologies for single step preparation of nitriles from the substrates like alcohols,[9] amines,[10] amides,[11] azides,[12] and oximes[13] are known. The other alternative approaches are olefinic bond cleavage of alkene,[14] cyanation of aryl halides,[15] oxidative rearrangement of alkene,[16] methyl arenes,[17] and benzyl or allyl halides.[18] Preparation of nitriles from aldehydes is one of the interesting and advantageous approaches because the number of carbon in reactant and final product will remain same. The main features of one-pot transformations are valuable strategic way in terms of economic and environmental aspects. One-pot reactions usually consist of two or more than two steps that has to be done in a single step without isolation of intermediate, which in turn, substantially help to reduces the energy consumption, solvent waste, and reaction time. Focusing on these advantages of one-pot synthesis, we planned to accomplish single step transformation of aldehydes into nitriles by means of minimum energy, chemicals waste, and small time outlay. The literature survey reveals that diverse catalytic systems have been applied for one-pot transformation of aldehydes into nitriles[19] but most of them are suffers from various constrain such as harsh reaction conditions, longer reaction time, low yield, work-up difficulties, and waste of toxic metal salt or solvents into the

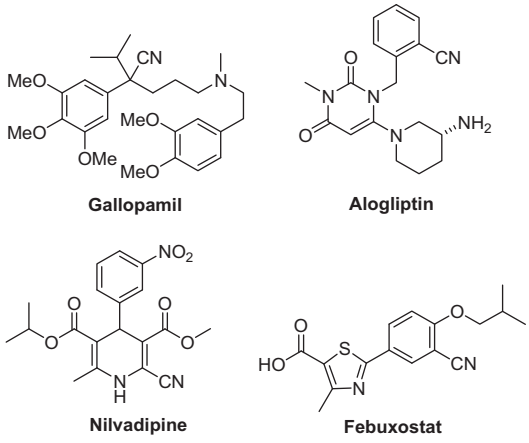

Figure 1. Potent bioactive organonitrile derivatives.

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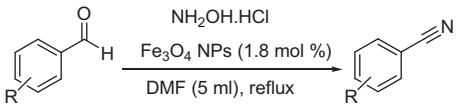


Scheme 1. Fe_3O_4 NPs catalyzed synthesis of nitriles from aldehydes.

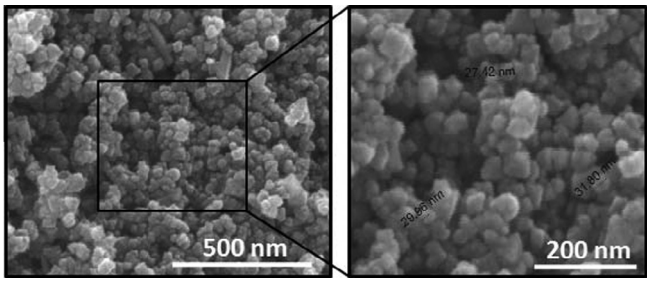


Figure 2a. FE-SEM images of Fe_3O_4-CTAB NPs.

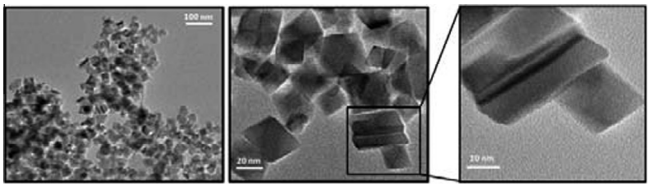


Figure 2b. TEM images of Fe_3O_4-CTAB NPs.

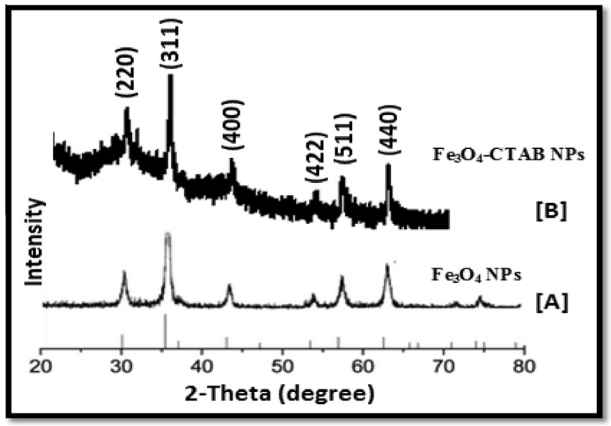


Figure 2c. Comparison of XRD pattern of Fe_3O_4-CTAB NPs [B] with the literature XRD pattern of pure Fe_3O_4 NPs [A].

environment. In view of our attempt to develop an efficient and environment friendly protocol, we have chosen Fe_3O_4-CTAB NPs catalyst for our present investigation. We believe that our investigation will definitely robust the synthetic approach and fulfill the paucity of sustainable development.

As iron oxide NPs are well documented in catalysis and medicinal chemistry.[20] The versatile catalytic activity, magnetic recyclability, low toxicity, and usefulness in medicinal chemistry made it environmentally and economically advantageous.[21] Easy accessibility and relatively low toxicity made iron NPs desirable nanocatalysts in present time. In our endevour to develop efficient protocol for nitrile synthesis, we report herein, Fe_3O_4-CTAB NPs catalyzed one-pot synthesis of organonitriles from aldehydes and hydroxylamine hydrochloride in DMF under reflux condition (Scheme 1).

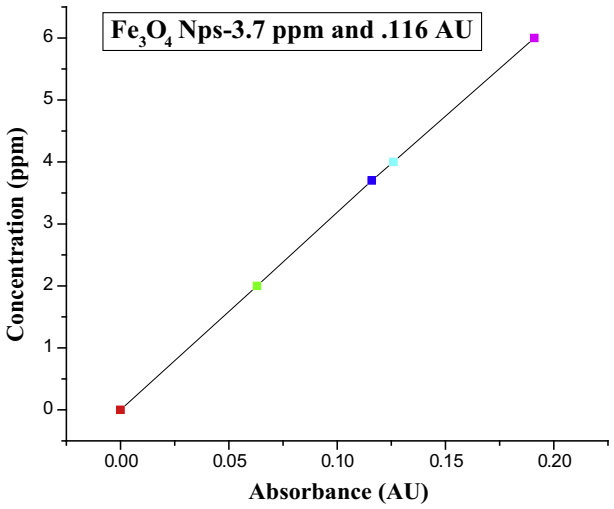


Figure 2d. AAS plot of absorbance versus concentration.

Table 1
Screening of catalytic activity of Fe_3O_4-CTAB NPs[a]

Entry	Fe_3O_4-CTAB (mg)	Fe_3O_4[b] (mol %)	Temp (°C)	Time (h)	Yield[c] (%)
1	23.1	7.4	rt	4	Nil
2	—	—	50	4	—
3	—	—	70	4	—
4	—	—	80	3	25
5	—	—	90	3	36
6	—	—	Reflux	2	97

[a] Reaction of vanillin (0.5 mmol), hydroxylamine hydrochloride (0.75 mmol), and Fe_3O_4-CTAB NPs (23.1 mg,) in dry DMF (5 ml) at different temperature.
[b] Amount of Fe_3O_4 NPs in Fe_3O_4-CTAB quantified by AAS.
[c] Isolated yield.

Table 2
Optimization of catalyst[a]

Entry	Fe_3O_4-CTAB (mg)	Fe_3O_4 (mol %)[b]	Time (h)	Yield (%)[c]
1	23.1	7.4	1.5	97
2	11.5	3.7	2	—
3	5.7	1.8	2	96
4	5.7	1.8	1.5	—
5	**5.7**	**1.8**	**1**	**96**[d]
6	5.7	1.8	0.5	91
7	3.4	0.9	2.5	88
8	2.3	0.6	4	83
9	1.1	0.3	4	78

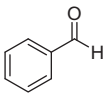
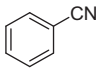
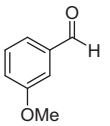
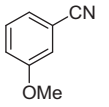
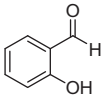
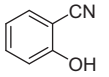
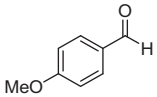
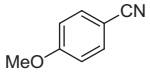
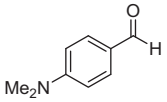
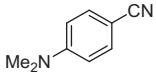
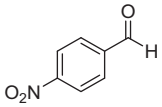
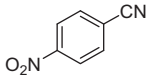
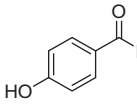
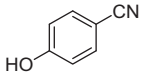
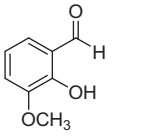
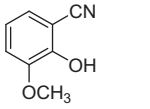
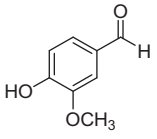
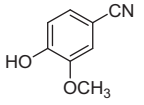
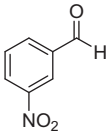
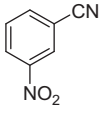
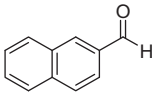
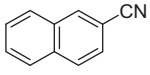
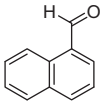
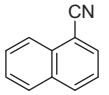
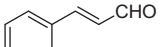
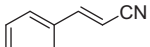
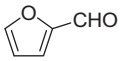
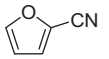
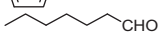
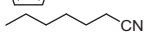
[a] Reaction of vanillin (0.5 mmol), hydroxylamine hydrochloride (0.75 mmol), and Fe_3O_4-CTAB NPs in dry DMF (5 ml) under reflux condition.
[b] Amount of Fe_3O_4 NPs in Fe_3O_4-CTAB quantified by AAS.
[c] Isolated yield.
[d] Optimized reaction condition.

Result and discussion

In continuation of our work for one-pot nitrile synthesis from aldehydes and hydroxylamine hydrochloride,[22] we used Fe_3O_4-CTAB NPs as catalyst for our present investigation. Fe_3O_4-CTAB NPs were synthesized by the reported method[23] (see Supporting information). The synthesized Fe_3O_4-CTAB NPs were then characterized by Field Emission Scanning Electron Microscope (FE-SEM, INSPECT F50, FEI), Transmission Electron Microscope

(TEM, JEOL, JEM 2100, 200 kV), and X-ray Diffraction (XRD, Advance D8, Bruker) analysis. FE-SEM images (Fig. 2a) reveal that the Fe_3O_4 NPs are 20–35 nm in size which is further confirmed by the TEM images (Fig. 2b). TEM images also reveal that the Fe_3O_4 NPs are in crystalline cubical shape. XRD spectra shows the standard peaks of the Fe_3O_4 are unhindered by the CTAB presence although peak broadening has occurred due to the nano-size of the Fe_3O_4. Moreover, we have compared XRD pattern of freshly prepared Fe_3O_4-CTAB NPs (Fig. 2c [B]) with the literature XRD pattern of pure Fe_3O_4 magnetite NPs (Fig. 2c [A]) and found exactly similar XRD pattern with Fe_3O_4 magnetite NPs. X-ray diffraction pattern of Fe_3O_4-CTAB also confirm the purity of magnetite via the absence of other phases of iron oxide such as maghemite or hematite in product. The quantification of Fe in Fe_3O_4-CTAB has been evaluated by Atomic Absorption Spectroscopy (AAS) using Fe standard solution as supplied by Sigma Aldrich. Figure 2d depicts the plot of absorbance versus concentration of Fe in Fe_3O_4-CTAB Nps. The concentration of Fe used during the calibration was 0, 2, 4, 6 ppm. The solution of Fe_3O_4-CTAB NPs in water was prepared by taking 5 mg of the sample in 100 ml water and the absorbance of the sample was taken. From the absorbance data, the concentration of Fe in Fe_3O_4-CTAB has been found to be 3.7 ppm (blue) and the percentage of Fe in Fe_3O_4-CTAB has been found to be 74% by weight.

Table 3
Fe_3O_4 NPs catalyzed synthesis of nitriles

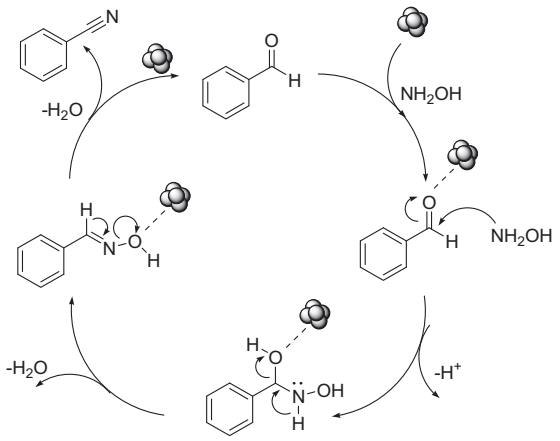
Entry	Aldehydes	Time (h)	Products	Yield[b] (%)
1		1		97
2		1		93
3		1.5		94
4		1.5		92
5		1.5		86
6		1		89
7		1.5		87
8		1		94
9		1		96
10		1.5		86
11		2		91
12		2		93
13		2		91
14		1.5		87
15		2		76

[b] Isolated yield.

In an endevor to begin our present investigation we have taken vanillin as our model compound. The model reaction comprised vanillin (0.5 mmol), hydroxylamine hydrochloride (0.75 mmol) and Fe_3O_4 NPs (7.4 mol %) in dry DMF (5 ml). The reactions were screened from room temperature to high temperature (Table 1). The excellent yield was found only at high temperature (entry 6, Table 1). The reaction at the temperature range between 50 and 70 °C furnish only oxime derivative and at 80–90 °C offered a mixture of oxime and nitriles derivatives.

After reaching satisfactory result under reflux condition in short reaction time (Table 1), the catalytic potential of Fe_3O_4-CTAB NPs was tested by reducing the amount of catalyst in similar reaction condition (Table 2). Finally we could optimize the reaction conditions and isolate 96% yield of nitrile in minimum reaction time (entry 5, Table 2). Further reduction of amount of catalyst or changing the reaction time could not produce a good result (entries 6–9, Table 2). The % of yield depends on both amount of catalyst and reaction temperature. The combination of aldehyde (0.5 mmol), hydroxylamine hydrochloride (0.75 mmol) and Fe_3O_4 NPs (1.8 mol %) in dry DMF (5 ml) under reflux condition was found to be the optimized reaction condition for the desired transformation (entry 5, Table 2). For the generalization of our scheme, aldehydes **1**–**15** were successfully converted into corresponding nitriles under optimized condition[24] (Table 3).

Plausible mechanism for Fe_3O_4-CTAB NPs catalyzed one-pot synthesis of nitriles from aldehydes is shown in Scheme 2. Fe_3O_4-CTAB NPs activate carbonyl carbon for nucleophilic attack by



Scheme 2. Plausible mechanism for the transformation of aldehyde into nitrile.

hydroxylamine. Subsequent deprotonation followed by loss of water molecule gives rise to the formation of oxime derivatives. Finally, Fe_3O_4-CTAB NPs participate in expulsion of water molecule from oxime to give the desired product and itself get regenerated at the end of reaction for consecutive cycles.

Conclusion

In conclusion, we have developed an Fe_3O_4-CTAB NPs catalyzed efficient protocol for one-pot conversion of aldehydes into nitriles from aldehydes (0.5 mmol), hydroxylamine hydrochloride (0.75 mmol) in dry DMF (5 ml) under reflux condition. Advantage of this protocol includes the use of inexpensive and relatively less toxic nanocatalyst, excellent yield, easy reaction setup, and easy work-up process.

Acknowledgement

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2016.06.125.

References and notes

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24. *General procedure for the synthesis of nitrile from aldehyde*: Aldehyde (0.5 mmol) and hydroxylamine hydrochloride (0.75 mmol) were added successively to a solution of Fe_3O_4-CTAB NPs (5.7 mg) i.e Fe_3O_4 (1.8 mol %) in 5 ml dry DMF. The mixture was reflux for appropriate time (Table 3). The progress of the reaction was monitored by TLC. After completion of the reaction, the solution was poured into 100 ml water and extract with ethyl acetate, washed several times with water. The combined organic mixture was dried over anhydrous Na_2SO_4, concentrated, and the residue was purified by column chromatography on silica gel 60–120 mesh using petroleum ether/ethyl acetate (95:5) as eluent to afford the pure nitrile. All the products were characterized by IR, ^{1}H NMR, and ^{13}C NMR.